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FILE 'HOME' ENTERED AT 18:07:12 ON 06 JUL 2001

=> file medline biosis biotechno

COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
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FULL ESTIMATED COST                                         0.15       0.15

FILE 'MEDLINE' ENTERED AT 18:07:22 ON 06 JUL 2001

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=> s (alanine scan?)

L1         1314 (ALANINE SCAN?)

=> s l1 and hedgehog

L2            0 L1 AND HEDGEHOG

=> s hedgehog

L3         4993 HEDGEHOG

=> s l1 and l3

L4            0 L1 AND L3

=> s l3 and mutageneis

L5            0 L3 AND MUTAGENEIS

=> s l3 and residues

L6           59 L3 AND RESIDUES

=> s l3 and muta?

L7         1081 L3 AND MUTA?

=> s mutagenesis

L8       131744 MUTAGENESIS

=> s l8 and l3

L9           58 L8 AND L3

=> dup rem l9

PROCESSING COMPLETED FOR L9
L10          46 DUP REM L9 (12 DUPLICATES REMOVED)

=> d ibib abs 1-15


L10  ANSWER 1 OF 46  MEDLINE                              DUPLICATE 1
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ACCESSION NUMBER: 20[redacted]07289 MEDLINE
DOCUMENT NUMBER: 21[redacted]771 PubMed ID: 11254125
TITLE: Essential genes in proximal 3L heterochromatin of Drosophila melanogaster.
AUTHOR: Schulze S; Sinclair D A; Silva E; Fitzpatrick K A; Singh M;
Lloyd V K; Morin K A; Kim J; Holm D G; Kennison J A; Honda B M
CORPORATE SOURCE: Department of Molecular Biology and Biochemistry, Simon Fraser University Burnaby, BC, Canada.
SOURCE: MOLECULAR AND GENERAL GENETICS, (2001 Feb) 264 (6) 782-9.
Journal code: NGP; 0125036. ISSN: 0026-8925.
PUB. COUNTRY: Germany: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20010417
Entered PubMed: 20010319
Entered Medline: 20010412

AB We have further characterized essential loci within the centric heterochromatin of the left arm of chromosome 3 (3L) of Drosophila melanogaster, using EMS, radiation and P element **mutagenesis**. We failed to find any new essential genes, a result that suggests a lower-than-average gene density in this region. Mutations affecting expression of the most proximal gene [lethal 1, 11 or l(3)80Fj] act as dominant suppressors of Polycomb (Pc), behavior which is consistent with a
putative trithorax group (trx-G) gene. The third gene to the left of the centromere [lethal 3, 13 or l(3)80Fh] is likely to correspond to verthandi
(vtd), a known trx-G gene that plays a role in the regulation of **hedgehog** (hh) expression and signalling. The intervening gene [lethal 2, 12 or l(3)80Fi] is required throughout development, and mutant alleles have interesting phenotypes; in various allelic combinations that survive, we observe fertility, bristle, wing, eye and cuticle defects.

L10 ANSWER 2 OF 46 MEDLINE
ACCESSION NUMBER: 2001338115 MEDLINE
DOCUMENT NUMBER: 21096921 PubMed ID: 11181569
TITLE: A Ser(365)-->Cys mutation of fibroblast growth factor receptor 3 in mouse downregulates Ihh/PTHrP signals and causes severe achondroplasia.
AUTHOR: Chen L; Li C; Qiao W; Xu X; Deng C
CORPORATE SOURCE: Genetics of Development and Disease Branch, Building 10, Room 9N105, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: HUMAN MOLECULAR GENETICS, (2001 Mar 1) 10 (5) 457-65.
Journal code: BRC; 9208958. ISSN: 0964-6906.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010618
Last Updated on STN: 20010618
Entered PubMed: 20010222
Entered Medline: 20010614

AB Missense mutations in fibroblast growth factor receptor 3 (FGFR3) result in several types of human skeletal dysplasia, including the neonatally lethal dwarfism known as thanatophoric dysplasia. An engineered Ser(365)-->Cys substitution in mouse FGFR3, which is equivalent to a mutation associated with thanatophoric dysplasia-I in humans, has now been
shown to cause severe dwarfism but not neonatal death. The mutant mice exhibit shortened limbs as a result of markedly reduced proliferation and

impaired differentiation of growth plate chondrocytes. The receptor-activating mutation also resulted in downregulation of expression of the Indian **hedgehog** (IHH) and parathyroid hormone-related protein (PTHrP) receptor genes, both of which are important for bone growth. Interactions between FGFR3- and PTHrP-receptor-mediated signals during endochondral ossification were examined with embryonic metatarsal bones maintained in culture under defined conditions. Consistent with the in vivo observations, FGF2 inhibited bone growth in culture and induced downregulation of IHH and PTHrP receptor gene expression. Furthermore, PTHrP partially reversed the inhibition of long bone growth caused by activation of FGFR3; however, it impaired the differentiation of chondrocytes in an FGFR3-independent manner. These observations suggest that FGFR3 and IHH-PTHrP signals are transmitted by two interacting parallel pathways that mediate both overlapping and distinct functions during endochondral ossification.

L10 ANSWER 3 OF 46 MEDLINE
ACCESSION NUMBER: 2001142264 MEDLINE
DOCUMENT NUMBER: 21094512 PubMed ID: 11182084
TITLE: Glial cells mediate target layer selection of retinal axons in the developing visual system of Drosophila.
AUTHOR: Poeck B; Fischer S; Gunning D; Zipursky S L; Salecker I
CORPORATE SOURCE: Lehrstuhl fur Entwicklungsbiologie, Institut fur Zoologie, Universitat Regensburg, Universitatsstr. 31, 93053, Regensburg, Germany.
SOURCE: NEURON, (2001 Jan) 29 (1) 99-113.
Journal code: AN8; 8809320. ISSN: 0896-6273.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF179590
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered PubMed: 20010222
Entered Medline: 20010308

AB In the fly visual system, each class of photoreceptor neurons (R cells) projects to a different synaptic layer in the brain. R1-R6 axons terminate in the lamina, while R7 and R8 axons pass through the lamina and stop in the medulla. As R cell axons enter the lamina, they encounter both glial cells and neurons. The cellular requirement for R1-R6 targeting was determined using loss-of-function mutations affecting different cell types in the lamina. nonstop (encoding a ubiquitin-specific protease) is required for glial cell development and **hedgehog** for neuronal development. Removal of glial cells but not neurons disrupts R1-R6 targeting. We propose that glial cells provide the initial stop signal promoting growth cone termination in the lamina. These findings uncover a novel function for neuron-glial interactions in regulating target specificity.

L10 ANSWER 4 OF 46 MEDLINE
ACCESSION NUMBER: 2001091541 MEDLINE
DOCUMENT NUMBER: 20515603 PubMed ID: 11060228
TITLE: The Gsh2 homeodomain gene controls multiple aspects of telencephalic development.
AUTHOR: Corbin J G; Gaiano N; Machold R P; Langston A; Fishell G
CORPORATE SOURCE: Developmental Genetics Program and the Department of Cell Biology, The Skirball Institute of Biomolecular Medicine, New York University Medical Center, New York, NY 10016, USA.. fishell@saturn.med.nyu.edu
CONTRACT NUMBER: NS10962-01 (NINDS)
NS39007 (NINDS)
SOURCE: DEVELOPMENT, (2000 Dec) 127 (23) 5007-20.
Journal code: ECW. ISSN: 0950-1991.

PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered PubMed: 20001226
Entered Medline: 20010125

AB Homeobox genes have recently been demonstrated to be important for the proper patterning of the mammalian telencephalon. One of these genes is Gsh2, whose expression in the forebrain is restricted to the ventral domain. In this study, we demonstrate that Gsh2 is a downstream target of sonic **hedgehog** and that lack of Gsh2 results in profound defects in telencephalic development. Gsh2 mutants have a significant decrease in the expression of numerous genes that mark early development of the lateral ganglionic eminence, the striatal anlage. Accompanying this early loss of patterning genes is an initial expansion of dorsal telencephalic markers across the cortical-striatal boundary into the lateral ganglionic eminence. Interestingly, as development proceeds, there is compensation for this early loss of markers that is coincident with a molecular re-establishment of the cortical-striatal boundary. Despite this compensation, there is a defect in the development of distinct subpopulations of striatal neurons. Moreover, while our analysis suggests that the migration of the ventrally derived interneurons to the developing cerebral cortex is not significantly affected in Gsh2 mutants, there is a distinct delay in the appearance of GABAergic interneurons in the olfactory bulb. Taken together, our data support a model in which Gsh2, in response to sonic **hedgehog** signaling, plays a crucial role in multiple aspects of telencephalic development.

L10 ANSWER 5 OF 46 MEDLINE
ACCESSION NUMBER: 2001045652 MEDLINE
DOCUMENT NUMBER: 20433230 PubMed ID: 10976042
TITLE: Transcriptional regulation of the **Hedgehog** effector CI by the zinc-finger gene combgap.
AUTHOR: Campbell G L; Tomlinson A
CORPORATE SOURCE: Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA 15260, USA.. camp@pitt.edu
SOURCE: DEVELOPMENT, (2000 Oct) 127 (19) 4095-103.
Journal code: ECW. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001201

AB Members of the **Hedgehog** (HH) family of secreted signaling molecules specify cell fate during animal development by controlling the activity of members of the Gli family of zinc-finger transcription factors in responding cells. In Drosophila the Gli homolog, cubitus interruptus (CI), is expressed only in the anterior compartment where it represses targets such as the signaling molecule genes decapentaplegic (dpp) and wingless (wg). HH is expressed in the posterior and diffuses into the anterior where it antagonizes CI repression resulting in dpp and wg expression immediately anterior to the compartment border. Reducing CI levels results in misexpression of wg and dpp, while CI misexpression in the posterior disrupts differentiation. Thus, normal disc patterning requires high levels of CI in the anterior and the absence of CI in the posterior. Here we show that mutations in combgap (cg) result in deregulation of CI expression, which is now expressed at much lower levels and ubiquitously, i.e., also in the posterior. Consequently, cg mutants phenocopy ci loss-of-function mutants in the anterior and ci

gain-of-function mutants in the posterior. cg encodes a putative DNA-binding protein that regulates both transcriptional activation and repression of the ci gene.

L10 ANSWER 6 OF 46 MEDLINE
ACCESSION NUMBER: 2000233839 MEDLINE
DOCUMENT NUMBER: 20233839 PubMed ID: 10769242
TITLE: The zebrafish slow-muscle-omitted gene product is required for **Hedgehog** signal transduction and the development of slow muscle identity.
AUTHOR: Barresi M J; Stickney H L; Devoto S H
CORPORATE SOURCE: Biology Department, Wesleyan University, Middletown, CT 06459, USA.
CONTRACT NUMBER: AR45575 (NIAMS)
HD22486 (NICHD)
HD37509-01 (NICHD)
SOURCE: DEVELOPMENT, (2000 May) 127 (10) 2189-99.
Journal code: ECW; 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000728
Last Updated on STN: 20000728
Entered Medline: 20000714

AB **Hedgehog** proteins mediate many of the inductive interactions that determine cell fate during embryonic development. **Hedgehog** signaling has been shown to regulate slow muscle fiber type development. We report here that mutations in the zebrafish slow-muscle-omitted (smu) gene disrupt many developmental processes involving **Hedgehog** signaling. smu(-/-) embryos have a 99% reduction in the number of slow muscle fibers and a complete loss of Engrailed-expressing muscle pioneers.

In addition, mutant embryos have partial cyclopia, and defects in jaw cartilage, circulation and fin growth. The smu(-/-) phenotype is phenocopied by treatment of wild-type embryos with forskolin, which inhibits the response of cells to **Hedgehog** signaling by indirect activation of cAMP-dependent protein kinase (PKA). Overexpression of Sonic **hedgehog** (Shh) or dominant negative PKA (dnPKA) in wild-type embryos causes all somitic cells to develop into slow muscle fibers. Overexpression of Shh does not rescue slow muscle fiber development in smu(-/-) embryos, whereas overexpression of dnPKA does. Cell transplantation experiments confirm that smu function is required cell-autonomously within the muscle precursors: wild-type muscle cells rescue slow muscle fiber development in smu(-/-) embryos, whereas mutant muscle cells cannot develop into slow muscle fibers in wild-type embryos. Slow muscle fiber development in smu mutant embryos is also rescued by expression of rat Smoothened. Therefore, **Hedgehog** signaling through Slow-muscle-omitted is necessary for slow muscle fiber type development. We propose that smu encodes a vital component in the **Hedgehog** response pathway.

L10 ANSWER 7 OF 46 MEDLINE
ACCESSION NUMBER: 2000233837 MEDLINE
DOCUMENT NUMBER: 20233837 PubMed ID: 10769240
TITLE: Regulation of cell proliferation and patterning in Drosophila oogenesis by **Hedgehog** signaling.
AUTHOR: Zhang Y; Kalderon D
CORPORATE SOURCE: Department of Biological Sciences, Columbia University, New York, NY 10027, USA.
CONTRACT NUMBER: GM41815 (NIGMS)
SOURCE: DEVELOPMENT, (2000 May) 127 (10) 2165-76.
Journal code: ECW; 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000728
Last Updated on STN: 20000728
Entered Medline: 20000714

AB The localized expression of **Hedgehog** (Hh) at the extreme anterior of Drosophila ovarioles suggests that it might provide an asymmetric cue that patterns developing egg chambers along the anteroposterior axis. Ectopic or excessive Hh signaling disrupts egg chamber patterning dramatically through primary effects at two developmental stages. First, excess Hh signaling in somatic stem cells stimulates somatic cell over-proliferation. This likely disrupts the earliest interactions between somatic and germline cells and may account for the frequent mis-positioning of oocytes within egg chambers. Second, the initiation of the developmental programs of follicle cell lineages appears to be delayed by ectopic Hh signaling. This may account for the formation of ectopic polar cells, the extended proliferation of follicle cells and the defective differentiation of posterior follicle cells, which, in turn, disrupts polarity within the oocyte. Somatic cells in the ovary cannot proliferate normally in the absence of Hh or Smoothened activity. Loss of protein kinase A activity restores the proliferation of somatic cells in the absence of Hh activity and allows the formation of normally patterned ovarioles. Hence, localized Hh is not essential to direct egg chamber patterning.

L10 ANSWER 8 OF 46 MEDLINE
ACCESSION NUMBER: 2000472349 MEDLINE
DOCUMENT NUMBER: 20428548 PubMed ID: 10970877
TITLE: Ventral neural patterning by Nkx homeobox genes: Nkx6.1 controls somatic motor neuron and ventral interneuron fates.
AUTHOR: Sander M; Paydar S; Ericson J; Briscoe J; Berber E; German M; Jessell T M; Rubenstein J L
CORPORATE SOURCE: Hormone Research Institute, Department of Medicine, University of California-San Francisco, San Franscisco, California 94143, USA.
CONTRACT NUMBER: DK41822 (NIDDK)
K02MH01046-01 (NIMH)
R01DA12462 (NIDA)
+
SOURCE: GENES AND DEVELOPMENT, (2000 Sep 1) 14 (17) 2134-9.
Journal code: FN3; 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20001012
Entered Medline: 20001003

AB There is growing evidence that sonic **hedgehog** (Shh) signaling regulates ventral neuronal fate in the vertebrate central nervous system through Nkx-class homeodomain proteins. We have examined the patterns of neurogenesis in mice carrying a targeted mutation in Nkx6.1. These mutants show a dorsal-to-ventral switch in the identity of progenitors and in the fate of postmitotic neurons. At many axial levels there is a complete block in the generation of V2 interneurons and motor neurons and a compensatory ventral expansion in the domain of generation of V1 neurons, demonstrating the essential functions of Nkx6.1 in regional patterning and neuronal fate determination.

L10 ANSWER 9 OF 46 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001115552 MEDLINE
DOCUMENT NUMBER: 20556145 PubMed ID: 11102373
TITLE: A directed **mutagenesis** screen in Drosophila melanogaster reveals new mutants that influence **hedgehog** signaling.

AUTHOR: Ha[redacted]s N; van den Heuvel M
CORPORATE SOURCE: MR[redacted]unctional Genetics Unit, Depar[redacted]nt of Human Anatomy and Genetics, University of Oxford, Oxford OX1 3QX, United Kingdom.
SOURCE: GENETICS, (2000 Dec) 156 (4) 1777-85.
Journal code: FNH. ISSN: 0016-6731.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered PubMed: 20001228
Entered Medline: 20010215

AB The **Hedgehog** signaling pathway has been recognized as essential for patterning processes in development of metazoan animal species. The signaling pathway is, however, not entirely understood. To start to address this problem, we set out to isolate new mutations that influence **Hedgehog** signaling. We performed a **mutagenesis** screen for mutations that dominantly suppress **Hedgehog** overexpression phenotypes in the Drosophila melanogaster wing. We isolated four mutations that influence **Hedgehog** signaling. These were analyzed in the amenable wing system using genetic and molecular techniques. One of these four mutations affects the stability of the **Hedgehog** expression domain boundary, also known as the organizer in the developing wing. Another mutation affects a possible **Hedgehog** autoregulation mechanism, which stabilizes the same boundary.

L10 ANSWER 10 OF 46 MEDLINE
ACCESSION NUMBER: 2000191741 MEDLINE
DOCUMENT NUMBER: 20191741 PubMed ID: 10725244
TITLE: Drosophila atonal controls photoreceptor R8-specific properties and modulates both receptor tyrosine kinase and **Hedgehog** signalling.
AUTHOR: White N M; Jarman A P
CORPORATE SOURCE: Institute of Cell and Molecular Biology, University of Edinburgh, King's Buildings, Edinburgh, EH9 3JR, UK.
SOURCE: DEVELOPMENT, (2000 Apr) 127 (8) 1681-9.
Journal code: ECW; 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000714
Last Updated on STN: 20000714
Entered Medline: 20000630

AB During Drosophila eye development, the proneural gene atonal specifies founding R8 photoreceptors of individual ommatidia, evenly spaced relative to one another in a pattern that prefigures ommatidial organisation in the mature compound eye. Beyond providing neural competence, however, it has remained unclear to what extent atonal controls specific R8 properties. We show here that reduced Atonal function gives rise to R8 photoreceptors that are functionally compromised: both recruitment and axon pathfinding defects are evident. Conversely, prolonged Atonal expression in R8 photoreceptors induces defects in inductive recruitment as a consequence of hyperactive EGFR signalling. Surprisingly, such prolonged expression also results in R8 pattern formation defects in a process associated with both **Hedgehog** and Receptor Tyrosine Kinase signalling. Our results strongly suggest that Atonal regulates signalling and other properties of R8 precursors.

L10 ANSWER 11 OF 46 MEDLINE
ACCESSION NUMBER: 2000191733 MEDLINE

DOCUMENT NUMBER: 20[illegible]1733 PubMed ID: 10725236
TITLE: M[illegible] Gli1 mutants are viable but h[illegible] defects in SHH signaling in combination with a Gli2 mutation.
AUTHOR: Park H L; Bai C; Platt K A; Matise M P; Beeghly A; Hui C C;
Nakashima M; Joyner A L
CORPORATE SOURCE: Howard Hughes Medical Institute and Developmental Genetics Program, Skirball Institute of Biomolecular Medicine, Department of Cell Biology and Physiology and Neuroscience,
New York University Medical School, New York, NY 10016, USA.
SOURCE: DEVELOPMENT, (2000 Apr) 127 (8) 1593-605.
Journal code: ECW; 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000714
Last Updated on STN: 20000714
Entered Medline: 20000630

AB The secreted factor Sonic **hedgehog** (SHH) is both required for and sufficient to induce multiple developmental processes, including ventralization of the CNS, branching morphogenesis of the lungs and anteroposterior patterning of the limbs. Based on analogy to the Drosophila Hh pathway, the multiple GLI transcription factors in vertebrates are likely to both transduce SHH signaling and repress Shh transcription. In order to discriminate between overlapping versus unique requirements for the three Gli genes in mice, we have produced a Gli1 mutant and analyzed the phenotypes of Gli1/Gli2 and Gli1/3 double mutants.

Gli3(xt) mutants have polydactyly and dorsal CNS defects associated with ectopic Shh expression, indicating GLI3 plays a role in repressing Shh. In contrast, Gli2 mutants have five digits, but lack a floorplate, indicating that it is required to transduce SHH signaling in some tissues. Remarkably, mice homozygous for a Gli1(zfd)mutation that deletes the exons encoding the DNA-binding domain are viable and appear normal. Transgenic mice expressing a GLI1 protein lacking the zinc fingers can not induce SHH targets in the dorsal brain, indicating that the Gli1(zfd)allele contains a hypomorphic or null mutation. Interestingly, Gli1(zfd/zfd);Gli2(zfd/+), but not Gli1(zfd/zfd);Gli3(zfd/+) double mutants have a severe phenotype; most Gli1(zfd/zfd);Gli2(zfd/+) mice die soon after birth and all have multiple defects including a variable loss of ventral spinal cord cells and smaller lungs that are similar to, but less extreme than, Gli2(zfd/zfd) mutants. Gli1/Gli2 double homozygous mutants have more extreme CNS and lung defects than Gli1(zfd/zfd);Gli2(zfd/+) mutants, however, in contrast to Shh mutants, ventrolateral neurons develop in the CNS and the limbs have 5 digits with an extra postaxial nubbin. These studies demonstrate that the zinc-finger DNA-binding domain of GLI1 protein is not required for SHH signaling in mouse. Furthermore, Gli1 and Gli2, but not Gli1 and Gli3, have extensive overlapping functions that are likely downstream of SHH signaling.

L10 ANSWER 12 OF 46 MEDLINE
ACCESSION NUMBER: 2000296724 MEDLINE
DOCUMENT NUMBER: 20296724 PubMed ID: 10837029
TITLE: Tissue- and stage-specific modulation of Wingless signaling
by the segment polarity gene lines.
AUTHOR: Hatini V; Bokor P; Goto-Mandeville R; DiNardo S
CORPORATE SOURCE: University of Pennsylvania School of Medicine, Department of Cell and Developmental Biology, Philadelphia, Pennsylvania 19104 USA.
CONTRACT NUMBER: GM45747 (NIGMS)
SOURCE: GENES AND DEVELOPMENT, (2000 Jun 1) 14 (11) 1364-76.

Journal code: FN3; 8711660. ISSN: 0[redacted]-9369.
PUB. COUNTRY: Un[redacted]d States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000810
Last Updated on STN: 20000810
Entered Medline: 20000724

AB Wnt signaling controls a variety of developmental programs but the mechanisms by which the same signal leads to distinct outputs remain unclear. To address this question, we identified stage-specific modulators of Wingless (Wg) signaling in the Drosophila embryonic epidermis. We show that lines (lin) is essential for Wg-dependent patterning in dorsal epidermis. lin encodes a novel protein that acts cell-autonomously, downstream or in parallel to Armadillo (Arm) and upstream of Wg-dependent target genes. Lin can accumulate in nuclei of cells signaled by Wg, suggesting that signaling promotes entry of Lin into the nucleus, where it cooperates with Arm and Pangolin. Thus, a stage-specific modulator is used to mediate Wg signaling activity in dorsal patterning. **Hedgehog** (Hh) controls half of the parasegmental pattern dorsally and antagonizes Wg function to do so. Lin can accumulate in the cytoplasm of cells signaled by Hh, suggesting that Hh antagonizes Wg function by prohibiting Lin from entering the nucleus.

L10 ANSWER 13 OF 46 MEDLINE
ACCESSION NUMBER: 2001069166 MEDLINE
DOCUMENT NUMBER: 20519454 PubMed ID: 11063695
TITLE: A screen for dominant modifiers of ro(Dom), a mutation that disrupts morphogenetic furrow progression in Drosophila, identifies groucho and hairless as regulators of atonal expression.
AUTHOR: Chanut F; Luk A; Heberlein U
CORPORATE SOURCE: Department of Anatomy, University of California, San Francisco, California 94143, USA.. chanut@itsa.ucsf.edu
CONTRACT NUMBER: EY11410 (NEI)
SOURCE: GENETICS, (2000 Nov) 156 (3) 1203-17.
Journal code: FNH. ISSN: 0016-6731.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered PubMed: 20001121
Entered Medline: 20010104

AB ro(Dom) is a dominant allele of rough (ro) that results in reduced eye size due to premature arrest in morphogenetic furrow (MF) progression. We found that the ro(Dom) stop-furrow phenotype was sensitive to the dosage of genes known to affect retinal differentiation, in particular members of the **hedgehog** (hh) signaling cascade. We demonstrate that ro(Dom) interferes with Hh's ability to induce the retina-specific proneural gene atonal (ato) in the MF and that normal eye size can be restored by providing excess Ato protein. We used ro(Dom) as a sensitive genetic background in which to identify mutations that affect hh signal transduction or regulation of ato expression. In addition to mutations in several unknown loci, we recovered multiple alleles of groucho (gro) and Hairless (H). Analysis of their phenotypes in somatic clones suggests that both normally act to restrict neuronal cell fate in the retina, although they control different aspects of ato's complex expression pattern.

L10 ANSWER 14 OF 46 MEDLINE

ACCESSION NUMBER: 2000456355 MEDLINE
DOCUMENT NUMBER: 20[redacted]285 PubMed ID: 10983991
TITLE: Posttranscriptional regulation of smoothened is part of a self-correcting mechanism in the **Hedgehog** signaling system.
AUTHOR: Alcedo J; Zou Y; Noll M
CORPORATE SOURCE: Institute for Molecular Biology, University of Zurich, Switzerland.
SOURCE: MOLECULAR CELL, (2000 Aug) 6 (2) 457-65.
Journal code: C5E; 9802571. ISSN: 1097-2765.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001005
Last Updated on STN: 20001012
Entered Medline: 20000928

AB **Hedgehog** signaling, mediated through its Patched-Smoothened receptor complex, is essential for pattern formation in animal development. Activating mutations within Smoothened have been associated with basal cell carcinoma, suggesting that smoothened is a protooncogene. Thus, regulation of Smoothened levels might be critical for normal development. We show that Smoothened protein levels in Drosophila embryos are regulated posttranscriptionally by a mechanism dependent on **Hedgehog** signaling but not on its nuclear effector Cubitus interruptus. **Hedgehog** signaling upregulates Smoothened levels, which are otherwise downregulated by Patched. Demonstrating properties of a self-correcting system, the **Hedgehog** signaling pathway adjusts the concentrations of Smoothened and Patched to each other and to that of the **Hedgehog** signal, which ensures that activation of **Hedgehog** target genes by Smoothened signaling becomes strictly dependent on **Hedgehog**.

L10 ANSWER 15 OF 46 MEDLINE
ACCESSION NUMBER: 2000253066 MEDLINE
DOCUMENT NUMBER: 20253066 PubMed ID: 10790336
TITLE: Drosophila arc encodes a novel adherens junction-associated
PDZ domain protein required for wing and eye development.
AUTHOR: Liu X; Lengyel J A
CORPORATE SOURCE: Department of Molecular, Cell, and Developmental Biology, University of California at Los Angeles, Los Angeles, California, 90095-1606, USA.
CONTRACT NUMBER: HD09948 (NICHD)
SOURCE: DEVELOPMENTAL BIOLOGY, (2000 May 15) 221 (2) 419-34.
Journal code: E7T; 0372762. ISSN: 0012-1606.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000620

AB Loss of arc function results in a downwardly curved wing and smaller eyes with a reduced number of ommatidia. Consistent with this phenotype, molecular analysis shows that arc mRNA and protein are expressed in the wing imaginal disc and in clusters of cells in the morphogenetic furrow of the eye imaginal disc. The 36-kb arc transcription unit contains 10 exons that are spliced to form a 5. 5-kb mRNA. The encoded Arc protein is 143,000 Da and contains two PDZ (PSD-95, Discs large, ZO-1) domains; there is no close structural similarity to other PDZ proteins. In addition to its expression in imaginal discs, arc is expressed during embryogenesis in epithelia undergoing morphogenesis, including the invaginating posterior midgut, evaginating Malpighian tubule buds, elongating hindgut,

invaginating salivary glands, intersegmental groove[redacted] and developing tracheae. Arc pro[redacted]n colocalizes with Armadillo ([redacted]a-catenin) to the apical (luminal) surface of these developing epithelia, indicating that it is associated with adherens junctions. Genes that are required for patterning of embryonic epithelia (e.g., tailless, Kruppel, fork head, and brachyenteron) or for progression of the morphogenetic furrow (i. e., **hedgehog**) are required to establish or maintain the regional expression of arc. Misexpression of arc in the eye imaginal discs results in rough and larger eyes with fused ommatidia. We propose that arc affects eye development by modulating adherens junctions of the developing ommatidium.

=> d his

(FILE 'HOME' ENTERED AT 18:07:12 ON 06 JUL 2001)

FILE 'MEDLINE, BIOSIS, BIOTECHNO' ENTERED AT 18:07:22 ON 06 JUL 2001

L1	1314	S	(ALANINE SCAN?)
L2	0	S	L1 AND HEDGEHOG
L3	4993	S	HEDGEHOG
L4	0	S	L1 AND L3
L5	0	S	L3 AND MUTAGENEIS
L6	59	S	L3 AND RESIDUES
L7	1081	S	L3 AND MUTA?
L8	131744	S	MUTAGENESIS
L9	58	S	L8 AND L3
L10	46		DUP REM L9 (12 DUPLICATES REMOVED)

=> s mutagenesis and hedgehog

L11 58 MUTAGENESIS AND HEDGEHOG

=> d ibib abs 1-15

L11 ANSWER 1 OF 58 MEDLINE
ACCESSION NUMBER: 2001338115 MEDLINE
DOCUMENT NUMBER: 21096921 PubMed ID: 11181569
TITLE: A Ser(365)-->Cys mutation of fibroblast growth factor receptor 3 in mouse downregulates Ihh/PTHrP signals and causes severe achondroplasia.
AUTHOR: Chen L; Li C; Qiao W; Xu X; Deng C
CORPORATE SOURCE: Genetics of Development and Disease Branch, Building 10, Room 9N105, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: HUMAN MOLECULAR GENETICS, (2001 Mar 1) 10 (5) 457-65. Journal code: BRC; 9208958. ISSN: 0964-6906.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010618
Last Updated on STN: 20010618
Entered PubMed: 20010222
Entered Medline: 20010614

AB Missense mutations in fibroblast growth factor receptor 3 (FGFR3) result in several types of human skeletal dysplasia, including the neonatally lethal dwarfism known as thanatophoric dysplasia. An engineered Ser(365)-->Cys substitution in mouse FGFR3, which is equivalent to a mutation associated with thanatophoric dysplasia-I in humans, has now been

shown to cause severe dwarfism but not neonatal death. The mutant mice exhibit shortened limbs as a result of markedly reduced proliferation and impaired differentiation of growth plate chondrocytes. The receptor-activating mutation also resulted in downregulation of expression of the Indian **hedgehog** (IHH) and parathyroid hormone-related protein (PTHrP) receptor genes, both of which are important for bone growth. Interactions between FGFR3- and PTHrP-receptor-mediated signals during endochondral ossification were examined with embryonic metatarsal bones maintained in culture under defined conditions. Consistent with the in vivo observations, FGF2 inhibited bone growth in culture and induced downregulation of IHH and PTHrP receptor gene expression. Furthermore, PTHrP partially reversed the inhibition of long bone growth caused by activation of FGFR3; however, it impaired the differentiation of chondrocytes in an FGFR3-independent manner. These observations suggest that FGFR3 and IHH-PTHrP signals are transmitted by two interacting parallel pathways that mediate both overlapping and distinct functions during endochondral ossification.

L11 ANSWER 2 OF 58 MEDLINE
ACCESSION NUMBER: 2001207289 MEDLINE
DOCUMENT NUMBER: 21148771 PubMed ID: 11254125
TITLE: Essential genes in proximal 3L heterochromatin of Drosophila melanogaster.
AUTHOR: Schulze S; Sinclair D A; Silva E; Fitzpatrick K A; Singh M; Lloyd V K; Morin K A; Kim J; Holm D G; Kennison J A; Honda B M
CORPORATE SOURCE: Department of Molecular Biology and Biochemistry, Simon Fraser University Burnaby, BC, Canada.
SOURCE: MOLECULAR AND GENERAL GENETICS, (2001 Feb) 264 (6) 782-9.
Journal code: NGP; 0125036. ISSN: 0026-8925.
PUB. COUNTRY: Germany: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20010417
Entered PubMed: 20010319
Entered Medline: 20010412

AB We have further characterized essential loci within the centric heterochromatin of the left arm of chromosome 3 (3L) of Drosophila melanogaster, using EMS, radiation and P element **mutagenesis**. We failed to find any new essential genes, a result that suggests a lower-than-average gene density in this region. Mutations affecting expression of the most proximal gene [lethal 1, 11 or l(3)80Fj] act as dominant suppressors of Polycomb (Pc), behavior which is consistent with a putative trithorax group (trx-G) gene. The third gene to the left of the centromere [lethal 3, 13 or l(3)80Fh] is likely to correspond to verthandi (vtd), a known trx-G gene that plays a role in the regulation of **hedgehog** (hh) expression and signalling. The intervening gene [lethal 2, 12 or l(3)80Fi] is required throughout development, and mutant alleles have interesting phenotypes; in various allelic combinations that survive, we observe fertility, bristle, wing, eye and cuticle defects.

L11 ANSWER 3 OF 58 MEDLINE
ACCESSION NUMBER: 2001142264 MEDLINE
DOCUMENT NUMBER: 21094512 PubMed ID: 11182084
TITLE: Glial cells mediate target layer selection of retinal axons in the developing visual system of Drosophila.
AUTHOR: Poeck B; Fischer S; Gunning D; Zipursky S L; Salecker I
CORPORATE SOURCE: Lehrstuhl fur Entwicklungsbiologie, Institut fur Zoologie, Universitat Regensburg, Universitatsstr. 31, 93053, Regensburg, Germany.

SOURCE: NEURON, (2001 Jan) 29 (1) 99-113.
Journal code: AN8; 8809320. ISSN: 0[redacted]-6273.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF179590
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered PubMed: 20010222
Entered Medline: 20010308

AB In the fly visual system, each class of photoreceptor neurons (R cells) projects to a different synaptic layer in the brain. R1-R6 axons terminate in the lamina, while R7 and R8 axons pass through the lamina and stop in the medulla. As R cell axons enter the lamina, they encounter both glial cells and neurons. The cellular requirement for R1-R6 targeting was determined using loss-of-function mutations affecting different cell types in the lamina. nonstop (encoding a ubiquitin-specific protease) is required for glial cell development and **hedgehog** for neuronal development. Removal of glial cells but not neurons disrupts R1-R6 targeting. We propose that glial cells provide the initial stop signal promoting growth cone termination in the lamina. These findings uncover a novel function for neuron-glial interactions in regulating target specificity.

L11 ANSWER 4 OF 58 MEDLINE
ACCESSION NUMBER: 2001115552 MEDLINE
DOCUMENT NUMBER: 20556145 PubMed ID: 11102373
TITLE: A directed **mutagenesis** screen in Drosophila melanogaster reveals new mutants that influence **hedgehog** signaling.
AUTHOR: Haines N; van den Heuvel M
CORPORATE SOURCE: MRC Functional Genetics Unit, Department of Human Anatomy and Genetics, University of Oxford, Oxford OX1 3QX, United Kingdom.
SOURCE: GENETICS, (2000 Dec) 156 (4) 1777-85.
Journal code: FNH. ISSN: 0016-6731.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered PubMed: 20001228
Entered Medline: 20010215

AB The **Hedgehog** signaling pathway has been recognized as essential for patterning processes in development of metazoan animal species. The signaling pathway is, however, not entirely understood. To start to address this problem, we set out to isolate new mutations that influence **Hedgehog** signaling. We performed a **mutagenesis** screen for mutations that dominantly suppress **Hedgehog** overexpression phenotypes in the Drosophila melanogaster wing. We isolated four mutations that influence **Hedgehog** signaling. These were analyzed in the amenable wing system using genetic and molecular techniques. One of these four mutations affects the stability of the **Hedgehog** expression domain boundary, also known as the organizer in the developing wing. Another mutation affects a possible **Hedgehog** autoregulation mechanism, which stabilizes the same boundary.

L11 ANSWER 5 OF 58 MEDLINE
ACCESSION NUMBER: 2001091541 MEDLINE
DOCUMENT NUMBER: 20515603 PubMed ID: 11060228
TITLE: The Gsh2 homeodomain gene controls multiple aspects of telencephalic development.

AUTHOR: Corbin J G; Gaiano N; Machold R P; Langston A; Fishell G
CORPORATE SOURCE: Developmental Genetics Program and Department of Cell Biology, The Skirball Institute of Biomolecular Medicine, New York University Medical Center, New York, NY 10016, USA.. fishell@saturn.med.nyu.edu
CONTRACT NUMBER: NS10962-01 (NINDS)
NS39007 (NINDS)
SOURCE: DEVELOPMENT, (2000 Dec) 127 (23) 5007-20.
Journal code: ECW. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered PubMed: 20001226
Entered Medline: 20010125

AB Homeobox genes have recently been demonstrated to be important for the proper patterning of the mammalian telencephalon. One of these genes is Gsh2, whose expression in the forebrain is restricted to the ventral domain. In this study, we demonstrate that Gsh2 is a downstream target of sonic **hedgehog** and that lack of Gsh2 results in profound defects in telencephalic development. Gsh2 mutants have a significant decrease in the expression of numerous genes that mark early development of the lateral ganglionic eminence, the striatal anlage. Accompanying this early loss of patterning genes is an initial expansion of dorsal telencephalic markers across the cortical-striatal boundary into the lateral ganglionic eminence. Interestingly, as development proceeds, there is compensation for this early loss of markers that is coincident with a molecular re-establishment of the cortical-striatal boundary. Despite this compensation, there is a defect in the development of distinct subpopulations of striatal neurons. Moreover, while our analysis suggests that the migration of the ventrally derived interneurons to the developing cerebral cortex is not significantly affected in Gsh2 mutants, there is a distinct delay in the appearance of GABAergic interneurons in the olfactory bulb. Taken together, our data support a model in which Gsh2, in response to sonic **hedgehog** signaling, plays a crucial role in multiple aspects of telencephalic development.

L11 ANSWER 6 OF 58 MEDLINE
ACCESSION NUMBER: 2001069166 MEDLINE
DOCUMENT NUMBER: 20519454 PubMed ID: 11063695
TITLE: A screen for dominant modifiers of ro(Dom), a mutation that disrupts morphogenetic furrow progression in Drosophila, identifies groucho and hairless as regulators of atonal expression.
AUTHOR: Chanut F; Luk A; Heberlein U
CORPORATE SOURCE: Department of Anatomy, University of California, San Francisco, California 94143, USA.. chanut@itsa.ucsf.edu
CONTRACT NUMBER: EY11410 (NEI)
SOURCE: GENETICS, (2000 Nov) 156 (3) 1203-17.
Journal code: FNH. ISSN: 0016-6731.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered PubMed: 20001121
Entered Medline: 20010104

AB ro(Dom) is a dominant allele of rough (ro) that results in reduced eye size due to premature arrest in morphogenetic furrow (MF) progression. We found that the ro(Dom) stop-furrow phenotype was sensitive to the dosage of genes known to affect retinal differentiation, in particular members of

the **hedgehog** (hh) signaling cascade. We demonstrate that ro(Dom) interferes with H[redacted] ability to induce the retina-[redacted]cific proneural gene atonal (ato) in the MF and that normal eye size can be restored by providing excess Ato protein. We used ro(Dom) as a sensitive genetic background in which to identify mutations that affect hh signal transduction or regulation of ato expression. In addition to mutations in several unknown loci, we recovered multiple alleles of groucho (gro) and Hairless (H). Analysis of their phenotypes in somatic clones suggests that both normally act to restrict neuronal cell fate in the retina, although they control different aspects of ato's complex expression pattern.

L11 ANSWER 7 OF 58 MEDLINE
ACCESSION NUMBER: 2001045652 MEDLINE
DOCUMENT NUMBER: 20433230 PubMed ID: 10976042
TITLE: Transcriptional regulation of the **Hedgehog** effector CI by the zinc-finger gene combgap.
AUTHOR: Campbell G L; Tomlinson A
CORPORATE SOURCE: Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA 15260, USA.. camp@pitt.edu
SOURCE: DEVELOPMENT, (2000 Oct) 127 (19) 4095-103.
Journal code: ECW. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001201

AB Members of the **Hedgehog** (HH) family of secreted signaling molecules specify cell fate during animal development by controlling the activity of members of the Gli family of zinc-finger transcription factors in responding cells. In Drosophila the Gli homolog, cubitus interruptus (CI), is expressed only in the anterior compartment where it represses targets such as the signaling molecule genes decapentaplegic (dpp) and wingless (wg). HH is expressed in the posterior and diffuses into the anterior where it antagonizes CI repression resulting in dpp and wg expression immediately anterior to the compartment border. Reducing CI levels results in misexpression of wg and dpp, while CI misexpression in the posterior disrupts differentiation. Thus, normal disc patterning requires high levels of CI in the anterior and the absence of CI in the posterior. Here we show that mutations in combgap (cg) result in deregulation of CI expression, which is now expressed at much lower levels and ubiquitously, i.e., also in the posterior. Consequently, cg mutants phenocopy ci loss-of-function mutants in the anterior and ci gain-of-function mutants in the posterior. cg encodes a putative DNA-binding protein that regulates both transcriptional activation and repression of the ci gene.

L11 ANSWER 8 OF 58 MEDLINE
ACCESSION NUMBER: 2000472349 MEDLINE
DOCUMENT NUMBER: 20428548 PubMed ID: 10970877
TITLE: Ventral neural patterning by Nkx homeobox genes: Nkx6.1 controls somatic motor neuron and ventral interneuron fates.
AUTHOR: Sander M; Paydar S; Ericson J; Briscoe J; Berber E; German M; Jessell T M; Rubenstein J L
CORPORATE SOURCE: Hormone Research Institute, Department of Medicine, University of California-San Francisco, San Franscisco, California 94143, USA.
CONTRACT NUMBER: DK41822 (NIDDK)
K02MH01046-01 (NIMH)
R01DA12462 (NIDA)
+
SOURCE: GENES AND DEVELOPMENT, (2000 Sep 1) 14 (17) 2134-9.
Journal code: FN3; 8711660. ISSN: 0890-9369.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20001012
Entered Medline: 20001003

AB There is growing evidence that sonic **hedgehog** (Shh) signaling regulates ventral neuronal fate in the vertebrate central nervous system through Nkx-class homeodomain proteins. We have examined the patterns of neurogenesis in mice carrying a targeted mutation in Nkx6.1. These mutants show a dorsal-to-ventral switch in the identity of progenitors and in the fate of postmitotic neurons. At many axial levels there is a complete block in the generation of V2 interneurons and motor neurons and a compensatory ventral expansion in the domain of generation of V1 neurons, demonstrating the essential functions of Nkx6.1 in regional patterning and neuronal fate determination.

L11 ANSWER 9 OF 58 MEDLINE
ACCESSION NUMBER: 2000456355 MEDLINE
DOCUMENT NUMBER: 20437285 PubMed ID: 10983991
TITLE: Posttranscriptional regulation of smoothened is part of a self-correcting mechanism in the **Hedgehog** signaling system.
AUTHOR: Alcedo J; Zou Y; Noll M
CORPORATE SOURCE: Institute for Molecular Biology, University of Zurich, Switzerland.
SOURCE: MOLECULAR CELL, (2000 Aug) 6 (2) 457-65.
Journal code: C5E; 9802571. ISSN: 1097-2765.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001005
Last Updated on STN: 20001012
Entered Medline: 20000928

AB **Hedgehog** signaling, mediated through its Patched-Smoothened receptor complex, is essential for pattern formation in animal development. Activating mutations within Smoothened have been associated with basal cell carcinoma, suggesting that smoothened is a protooncogene. Thus, regulation of Smoothened levels might be critical for normal development. We show that Smoothened protein levels in Drosophila embryos are regulated posttranscriptionally by a mechanism dependent on **Hedgehog** signaling but not on its nuclear effector Cubitus interruptus. **Hedgehog** signaling upregulates Smoothened levels, which are otherwise downregulated by Patched. Demonstrating properties of a self-correcting system, the **Hedgehog** signaling pathway adjusts the concentrations of Smoothened and Patched to each other and to that of the **Hedgehog** signal, which ensures that activation of **Hedgehog** target genes by Smoothened signaling becomes strictly dependent on **Hedgehog**.

L11 ANSWER 10 OF 58 MEDLINE
ACCESSION NUMBER: 2000296724 MEDLINE
DOCUMENT NUMBER: 20296724 PubMed ID: 10837029
TITLE: Tissue- and stage-specific modulation of Wingless signaling by the segment polarity gene lines.
AUTHOR: Hatini V; Bokor P; Goto-Mandeville R; DiNardo S
CORPORATE SOURCE: University of Pennsylvania School of Medicine, Department of Cell and Developmental Biology, Philadelphia, Pennsylvania 19104 USA.
CONTRACT NUMBER: GM45747 (NIGMS)
SOURCE: GENES AND DEVELOPMENT, (2000 Jun 1) 14 (11) 1364-76.
Journal code: FN3; 8711660. ISSN: 0890-9369.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000810
Last Updated on STN: 20000810
Entered Medline: 20000724

AB Wnt signaling controls a variety of developmental programs but the mechanisms by which the same signal leads to distinct outputs remain unclear. To address this question, we identified stage-specific modulators of Wingless (Wg) signaling in the Drosophila embryonic epidermis. We show that lines (lin) is essential for Wg-dependent patterning in dorsal epidermis. lin encodes a novel protein that acts cell-autonomously, downstream or in parallel to Armadillo (Arm) and upstream of Wg-dependent target genes. Lin can accumulate in nuclei of cells signaled by Wg, suggesting that signaling promotes entry of Lin into the nucleus, where it cooperates with Arm and Pangolin. Thus, a stage-specific modulator is used to mediate Wg signaling activity in dorsal patterning. **Hedgehog** (Hh) controls half of the parasegmental pattern dorsally and antagonizes Wg function to do so. Lin can accumulate in the cytoplasm of cells signaled by Hh, suggesting that Hh antagonizes Wg function by prohibiting Lin from entering the nucleus.

L11 ANSWER 11 OF 58 MEDLINE
ACCESSION NUMBER: 2000253066 MEDLINE
DOCUMENT NUMBER: 20253066 PubMed ID: 10790336
TITLE: Drosophila arc encodes a novel adherens junction-associated PDZ domain protein required for wing and eye development.
AUTHOR: Liu X; Lengyel J A
CORPORATE SOURCE: Department of Molecular, Cell, and Developmental Biology, University of California at Los Angeles, Los Angeles, California, 90095-1606, USA.
CONTRACT NUMBER: HD09948 (NICHD)
SOURCE: DEVELOPMENTAL BIOLOGY, (2000 May 15) 221 (2) 419-34.
Journal code: E7T; 0372762. ISSN: 0012-1606.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000620

AB Loss of arc function results in a downwardly curved wing and smaller eyes with a reduced number of ommatidia. Consistent with this phenotype, molecular analysis shows that arc mRNA and protein are expressed in the wing imaginal disc and in clusters of cells in the morphogenetic furrow of the eye imaginal disc. The 36-kb arc transcription unit contains 10 exons that are spliced to form a 5. 5-kb mRNA. The encoded Arc protein is 143,000 Da and contains two PDZ (PSD-95, Discs large, ZO-1) domains; there is no close structural similarity to other PDZ proteins. In addition to its expression in imaginal discs, arc is expressed during embryogenesis in epithelia undergoing morphogenesis, including the invaginating posterior midgut, evaginating Malpighian tubule buds, elongating hindgut, invaginating salivary glands, intersegmental grooves, and developing tracheae. Arc protein colocalizes with Armadillo (beta-catenin) to the apical (luminal) surface of these developing epithelia, indicating that it is associated with adherens junctions. Genes that are required for patterning of embryonic epithelia (e.g., tailless, Kruppel, fork head, and

brachyenteron) or for progression of the morphogenetic furrow (i. e., **hedgehog**) are required to establish or maintain the regional expression of arc. Misexpression of arc in the eye imaginal discs results in rough and larger eyes with fused ommatidia. We propose that arc affects eye development by modulating adherens junctions of the developing ommatidium.

L11 ANSWER 12 OF 58 MEDLINE
ACCESSION NUMBER: 2000253063 MEDLINE
DOCUMENT NUMBER: 20253063 PubMed ID: 10790333
TITLE: A transient specialization of the microtubule cytoskeleton is required for differentiation of the Drosophila visual system.
AUTHOR: Hoyle H D; Turner F R; Raff E C
CORPORATE SOURCE: Department of Biology and Institute for Molecular Biology, Indiana University, Bloomington, Indiana, 47405, USA.. hhoyle@bio.indiana.edu
SOURCE: DEVELOPMENTAL BIOLOGY, (2000 May 15) 221 (2) 375-89. Journal code: E7T; 0372762. ISSN: 0012-1606.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000620

AB Drosophila beta3-tubulin is an essential isoform expressed during differentiation of many cell types in embryos and pupae. We report here that during pupal development transient beta3 expression demarcates a unique subset of neurons in the developing adult visual system. beta3 is coassembled into microtubules with beta1, the sole beta-tubulin isoform in the permanent microtubule cytoskeleton of the adult eye and brain. Examination of beta3 mutant phenotypes showed that beta3 is required for axonal patterning and connectivity and for spatial positioning within the optic lobe. Comparison of the phenotypes of beta3 mutations with those that result from disruption of the **Hedgehog** signaling pathway shows that beta3 functions early in the establishment of the adult visual system. Our data support the hypothesis that beta3 confers specialized properties on the microtubules into which it is incorporated. Thus a transient specialization of the microtubule cytoskeleton during differentiation of a specific subset of the neurons has permanent consequences for later cell function.

L11 ANSWER 13 OF 58 MEDLINE
ACCESSION NUMBER: 2000233839 MEDLINE
DOCUMENT NUMBER: 20233839 PubMed ID: 10769242
TITLE: The zebrafish slow-muscle-omitted gene product is required for **Hedgehog** signal transduction and the development of slow muscle identity.
AUTHOR: Barresi M J; Stickney H L; Devoto S H
CORPORATE SOURCE: Biology Department, Wesleyan University, Middletown, CT 06459, USA.
CONTRACT NUMBER: AR45575 (NIAMS)
HD22486 (NICHD)
HD37509-01 (NICHD)
SOURCE: DEVELOPMENT, (2000 May) 127 (10) 2189-99. Journal code: ECW; 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000728
Last Updated on STN: 20000728

Entered Medline: 20000714

AB **Hedgehog** proteins mediate many of the inductive interactions that determine cell fate during embryonic development. **Hedgehog** signaling has been shown to regulate slow muscle fiber type development. We report here that mutations in the zebrafish slow-muscle-omitted (smu) gene disrupt many developmental processes involving **Hedgehog** signaling. smu(-/-) embryos have a 99% reduction in the number of slow muscle fibers and a complete loss of Engrailed-expressing muscle pioneers.

In addition, mutant embryos have partial cyclopia, and defects in jaw cartilage, circulation and fin growth. The smu(-/-) phenotype is phenocopied by treatment of wild-type embryos with forskolin, which inhibits the response of cells to **Hedgehog** signaling by indirect activation of cAMP-dependent protein kinase (PKA). Overexpression of Sonic **hedgehog** (Shh) or dominant negative PKA (dnPKA) in wild-type embryos causes all somitic cells to develop into slow muscle fibers. Overexpression of Shh does not rescue slow muscle fiber development in smu(-/-) embryos, whereas overexpression of dnPKA does. Cell transplantation experiments confirm that smu function is required cell-autonomously within the muscle precursors: wild-type muscle cells rescue slow muscle fiber development in smu(-/-) embryos, whereas mutant muscle cells cannot develop into slow muscle fibers in wild-type embryos. Slow muscle fiber development in smu mutant embryos is also rescued by expression of rat Smoothened. Therefore, **Hedgehog** signaling through Slow-muscle-omitted is necessary for slow muscle fiber type development. We propose that smu encodes a vital component in the **Hedgehog** response pathway.

L11 ANSWER 14 OF 58 MEDLINE

ACCESSION NUMBER: 2000233837 MEDLINE
DOCUMENT NUMBER: 20233837 PubMed ID: 10769240
TITLE: Regulation of cell proliferation and patterning in Drosophila oogenesis by **Hedgehog** signaling.
AUTHOR: Zhang Y; Kalderon D
CORPORATE SOURCE: Department of Biological Sciences, Columbia University, New York, NY 10027, USA.
CONTRACT NUMBER: GM41815 (NIGMS)
SOURCE: DEVELOPMENT, (2000 May) 127 (10) 2165-76. Journal code: ECW; 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000728
Last Updated on STN: 20000728
Entered Medline: 20000714

AB The localized expression of **Hedgehog** (Hh) at the extreme anterior of Drosophila ovarioles suggests that it might provide an asymmetric cue that patterns developing egg chambers along the anteroposterior axis. Ectopic or excessive Hh signaling disrupts egg chamber patterning dramatically through primary effects at two developmental stages. First, excess Hh signaling in somatic stem cells stimulates somatic cell over-proliferation. This likely disrupts the earliest interactions between somatic and germline cells and may account for the frequent mis-positioning of oocytes within egg chambers. Second, the initiation of the developmental programs of follicle cell lineages appears to be delayed by ectopic Hh signaling. This may account for the formation of ectopic polar cells, the extended proliferation of follicle cells and the defective differentiation of posterior follicle cells, which, in turn, disrupts polarity within the oocyte. Somatic cells in the ovary cannot proliferate normally in the absence of Hh or Smoothened activity. Loss of protein kinase A activity restores the proliferation of somatic cells in the absence of Hh activity and allows the formation of normally patterned ovarioles. Hence, localized Hh is not essential to direct egg chamber patterning.

L11 ANSWER 15 OF 58 MEDLINE
ACCESSION NUMBER: 20[redacted]11955 MEDLINE
DOCUMENT NUMBER: 20211955 PubMed ID: 10744976
TITLE: The progeny of wingless-expressing cells deliver the signal
at a distance in Drosophila embryos.
AUTHOR: Pfeiffer S; Alexandre C; Calleja M; Vincent J P
CORPORATE SOURCE: National Institute for Medical Research, London, NW7 1AA, UK.
SOURCE: CURRENT BIOLOGY, (2000 Mar 23) 10 (6) 321-4.
Journal code: B44; 9107782. ISSN: 0960-9822.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000619

AB Pattern formation in developing animals requires that cells exchange signals mediated by secreted proteins. How these signals spread is still unclear. It is generally assumed that they reach their target site either by diffusion or active transport (reviewed in [1] [2]). Here, we report an alternative mode of transport for Wingless (Wg), a member of the Wnt family of signaling molecules. In embryos of the fruit fly Drosophila, the wingless (wg) gene is transcribed in narrow stripes of cells abutting the source of **Hedgehog** protein. We found that these cells or their progeny are free to roam towards the anterior. As they do so, they no longer receive the **Hedgehog** signal and stop transcribing wg. The cells leaving the expression domain retain inherited Wg protein in secretory vesicles, however, and carry it forwards over a distance of up to four cell diameters. Experiments using a membrane-tethered form of Wg showed that this mechanism is sufficient to account for the normal range of Wg. Nevertheless, evidence exists that Wg can also reach distant target cells independently of protein inheritance, possibly by restricted diffusion. We suggest that both transport mechanisms operate in wild-type embryos.

=> d ibib abs 16-26

L11 ANSWER 16 OF 58 MEDLINE
ACCESSION NUMBER: 2000191741 MEDLINE
DOCUMENT NUMBER: 20191741 PubMed ID: 10725244
TITLE: Drosophila atonal controls photoreceptor R8-specific properties and modulates both receptor tyrosine kinase and **Hedgehog** signalling.
AUTHOR: White N M; Jarman A P
CORPORATE SOURCE: Institute of Cell and Molecular Biology, University of Edinburgh, King's Buildings, Edinburgh, EH9 3JR, UK.
SOURCE: DEVELOPMENT, (2000 Apr) 127 (8) 1681-9.
Journal code: ECW; 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000714
Last Updated on STN: 20000714
Entered Medline: 20000630

AB During Drosophila eye development, the proneural gene atonal specifies founding R8 photoreceptors of individual ommatidia, evenly spaced relative to one another in a pattern that prefigures ommatidial organisation in the

mature compound eye. Beyond providing neural competence, however, it has remained unclear to what extent atonal controls specific R8 properties. We show here that reduced Atonal function gives rise to R8 photoreceptors that are functionally compromised: both recruitment and axon pathfinding defects are evident. Conversely, prolonged Atonal expression in R8 photoreceptors induces defects in inductive recruitment as a consequence of hyperactive EGFR signalling. Surprisingly, such prolonged expression also results in R8 pattern formation defects in a process associated with both **Hedgehog** and Receptor Tyrosine Kinase signalling. Our results strongly suggest that Atonal regulates signalling and other properties of R8 precursors.

L11 ANSWER 17 OF 58 MEDLINE
ACCESSION NUMBER: 2000191733 MEDLINE
DOCUMENT NUMBER: 20191733 PubMed ID: 10725236
TITLE: Mouse Gli1 mutants are viable but have defects in SHH signaling in combination with a Gli2 mutation.
AUTHOR: Park H L; Bai C; Platt K A; Matise M P; Beeghly A; Hui C C; Nakashima M; Joyner A L
CORPORATE SOURCE: Howard Hughes Medical Institute and Developmental Genetics Program, Skirball Institute of Biomolecular Medicine, Department of Cell Biology and Physiology and Neuroscience, New York University Medical School, New York, NY 10016, USA.
SOURCE: DEVELOPMENT, (2000 Apr) 127 (8) 1593-605. Journal code: ECW; 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000714
Last Updated on STN: 20000714
Entered Medline: 20000630

AB The secreted factor Sonic **hedgehog** (SHH) is both required for and sufficient to induce multiple developmental processes, including ventralization of the CNS, branching morphogenesis of the lungs and anteroposterior patterning of the limbs. Based on analogy to the Drosophila Hh pathway, the multiple GLI transcription factors in vertebrates are likely to both transduce SHH signaling and repress Shh transcription. In order to discriminate between overlapping versus unique requirements for the three Gli genes in mice, we have produced a Gli1 mutant and analyzed the phenotypes of Gli1/Gli2 and Gli1/3 double mutants.
Gli3(xt) mutants have polydactyly and dorsal CNS defects associated with ectopic Shh expression, indicating GLI3 plays a role in repressing Shh. In contrast, Gli2 mutants have five digits, but lack a floorplate, indicating that it is required to transduce SHH signaling in some tissues. Remarkably, mice homozygous for a Gli1(zfd)mutation that deletes the exons encoding the DNA-binding domain are viable and appear normal. Transgenic mice expressing a GLI1 protein lacking the zinc fingers can not induce SHH targets in the dorsal brain, indicating that the Gli1(zfd)allele contains a hypomorphic or null mutation. Interestingly, Gli1(zfd/zfd);Gli2(zfd/+), but not Gli1(zfd/zfd);Gli3(zfd/+) double mutants have a severe phenotype; most Gli1(zfd/zfd);Gli2(zfd/+) mice die soon after birth and all have multiple defects including a variable loss of ventral spinal cord cells and smaller lungs that are similar to, but less extreme than, Gli2(zfd/zfd) mutants. Gli1/Gli2 double homozygous mutants have more extreme CNS and lung defects than Gli1(zfd/zfd);Gli2(zfd/+) mutants, however, in contrast to Shh mutants, ventrolateral neurons develop in the CNS and the limbs have 5 digits with an extra postaxial nubbin. These studies demonstrate that the zinc-finger DNA-binding domain of GLI1 protein is not required for SHH signaling in

mouse. Furthermore, Gli1 and Gli2, but not Gli1 and Gli3, have extensive overlapping functions that are likely downstream of HH signaling.

L11 ANSWER 18 OF 58 MEDLINE
ACCESSION NUMBER: 2000026162 MEDLINE
DOCUMENT NUMBER: 20026162 PubMed ID: 10557210
TITLE: Protein kinase A antagonizes **Hedgehog** signaling by regulating both the activator and repressor forms of Cubitus interruptus.
AUTHOR: Wang G; Wang B; Jiang J
CORPORATE SOURCE: Center for Developmental Biology and Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, Texas 75235-9133, USA.
SOURCE: GENES AND DEVELOPMENT, (1999 Nov 1) 13 (21) 2828-37. Journal code: FN3; 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991222

AB The **Hedgehog** (Hh) family of secreted proteins controls many aspects of animal development. In Drosophila, Hh transduces its signal via Cubitus interruptus (Ci), a transcription factor present in two forms: a full-length activator and a carboxy-terminally truncated repressor that is derived from the full-length form by proteolytic processing. The proteolytic processing of Ci is promoted by the activities of protein kinase A (PKA) and Slimb, whereas it is inhibited by Hh. Here we show that PKA inhibits the activity of the full-length Ci in addition to its role in regulating Ci proteolysis. Whereas Ci processing is blocked in both PKA and slimb mutant cells, the accumulated full-length Ci becomes activated only in PKA but not in slimb mutant cells. Moreover, PKA inhibits an uncleavable activator form of Ci. These observations suggest that PKA regulates the activity of the full-length Ci independent of its proteolytic processing. We also provide evidence that PKA regulates both the proteolytic processing and transcriptional activity of Ci by directly phosphorylating Ci. We propose that phosphorylation of Ci by PKA has two separable roles: (1) It blocks the transcription activity of the full-length activator form of Ci, and (2) it targets Ci for Slimb-mediated proteolytic processing to generate the truncated form that functions as a repressor.

L11 ANSWER 19 OF 58 MEDLINE
ACCESSION NUMBER: 2000025757 MEDLINE
DOCUMENT NUMBER: 20025757 PubMed ID: 10556296
TITLE: The mutational spectrum of the sonic **hedgehog** gene in holoprosencephaly: SHH mutations cause a significant proportion of autosomal dominant holoprosencephaly.
AUTHOR: Nanni L; Ming J E; Bocian M; Steinhaus K; Bianchi D W; Die-Smulders C; Giannotti A; Imaizumi K; Jones K L; Campo M D; Martin R A; Meinecke P; Pierpont M E; Robin N H; Young I D; Roessler E; Muenke M
CORPORATE SOURCE: Departments of Pediatrics and Genetics, The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, PA 19104-4399, USA.
CONTRACT NUMBER: HD01218 (NICHD)
HD28732 (NICHD)
HD29862 (NICHD)

SOURCE: HUMAN MOLECULAR GENETICS, (1999 Dec (13) 2479-88.
Journal code: BRC; 9208958. ISSN: 0 -6906.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000124

AB Holoprosencephaly (HPE) is a common developmental anomaly of the human forebrain and midface where the cerebral hemispheres fail to separate into distinct left and right halves. We have previously reported haploinsufficiency for Sonic **Hedgehog** (SHH) as a cause for HPE. We have now performed mutational analysis of the complete coding region and intron-exon junctions of the SHH gene in 344 unrelated affected individuals. Herein, we describe 13 additional unrelated affected individuals with SHH mutations, including nonsense and missense mutations, deletions and an insertion. These mutations occur throughout the extent of the gene. No specific genotype-phenotype association is evident based on the correlation of the type or position of the mutations. In conjunction with our previous studies, we have identified a total of 23 mutations in 344 unrelated cases of HPE. They account for 14 cases of familial HPE and nine cases of sporadic HPE. Mutations in SHH were detected in 10 of 27 (37%) families showing autosomal dominant transmission of the HPE spectrum, based on structural anomalies. Interestingly, three of the patients with an SHH mutation also had abnormalities in another gene that is expressed during forebrain development. We suggest that the interactions of multiple gene products and/or environmental elements may determine the final phenotypic outcome for a given individual and that variations among these factors may cause the wide variability in the clinical features seen in HPE.

L11 ANSWER 20 OF 58 MEDLINE
ACCESSION NUMBER: 2000025417 MEDLINE
DOCUMENT NUMBER: 20025417 PubMed ID: 10555969
TITLE: Zinc-dependent structural stability of human Sonic **hedgehog**.
AUTHOR: Day E S; Wen D; Garber E A; Hong J; Avedissian L S; Rayhorn P; Shen W; Zeng C; Bailey V R; Reilly J O; Roden J A; Moore C B; Williams K P; Galdes A; Whitty A; Baker D P
CORPORATE SOURCE: Biogen Inc., 14 Cambridge Center, Cambridge, Massachusetts 02142, USA.
SOURCE: BIOCHEMISTRY, (1999 Nov 9) 38 (45) 14868-80.
Journal code: A0G; 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991220

AB The role of the zinc site in the N-terminal fragment of human Sonic **hedgehog** (ShhN) was explored by comparing the biophysical and functional properties of wild-type ShhN with those of mutants in which the zinc-coordinating residues H140, D147, and H182, or E176 which interacts with the metal ion via a bridging water molecule, were mutated to alanine.
The wild-type and E176A mutant proteins retained 1 mol of zinc/mol of protein after extensive dialysis, whereas the H140A and D147A mutants retained only 0.03 and 0.05 mol of zinc/mol of protein, respectively.

Assay of the wild[redacted]pe and mutant proteins in two [redacted]ivity assays indicated that th[redacted]ild-type and E176A mutant prot[redacted]s had similar activity, whereas the H140A and D147A mutants were significantly less active. These assays also indicated that the H140A and D147A mutants were susceptible to proteolysis. CD, fluorescence, and (1)H NMR spectra of the H140A, D147A, and E176A mutants measured at 20 or 25 degrees C were very similar to those observed for wild-type ShhN. However, CD measurements at 37 degrees C showed evidence of some structural differences in the H140A and D147A mutants. Guanidine hydrochloride (GuHCl) denaturation studies revealed that the loss of zinc from the H140A and D147A mutants destabilized the folded proteins by approximately 3.5 kcal/mol, comparable to the effect of removing zinc from wild-type ShhN by treatment with EDTA. Thermal melting curves of wild-type ShhN gave a single unfolding transition with a midpoint T(m) of approximately 59 degrees C, whereas both the H140A and D147A mutants displayed two distinct transitions with T(m) values of 37-38 and 52-54 degrees C, similar to that observed for EDTA-treated wild-type ShhN. Addition of zinc to the H140A and D147A mutants resulted in a partial restoration of stability against thermal and GuHCl denaturation. The ability of these mutants to bind zinc was confirmed using a fluorescence-based binding assay that indicated that they bound zinc with K(d) values of approximately 1.6 and approximately 15 nM, respectively, as compared to a value of </=100 pM for wild-type ShhN. The properties of the E176A mutant were indistinguishable from those of wild-type ShhN in all biophysical and functional assays, indicating that this residue does not contribute significantly to stabilization of the zinc-binding site and that ShhN does not require hydrolase activity for in vitro biological function.

L11 ANSWER 21 OF 58 MEDLINE
ACCESSION NUMBER: 2000005398 MEDLINE
DOCUMENT NUMBER: 20005398 PubMed ID: 10537006
TITLE: Ultraviolet radiation **mutagenesis** of **hedgehog** pathway genes in basal cell carcinomas.
AUTHOR: Aszterbaum M; Beech J; Epstein E H Jr
CORPORATE SOURCE: Department of Dermatology, University of California, San Francisco 94110, USA.. Aszterbaum@orca.ucsf.edu
CONTRACT NUMBER: AR39959 (NIAMS)
AR43119 (NIAMS)
SOURCE: JOURNAL OF INVESTIGATIVE DERMATOLOGY. SYMPOSIUM PROCEEDINGS, (1999 Sep) 4 (1) 41-5. Ref: 52
Journal code: C0U; 9609059. ISSN: 1087-0024.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991117

AB The identification of mutations in **Hedgehog** (HH) pathway genes in some basal cell carcinomas (BCC) and the detection of HH pathway dysregulation in almost all BCC confirms the importance of this developmental regulatory pathway in human BCC tumorigenesis. Moreover, the occurrence of UVB signature mutations in key HH pathway genes in BCC provides the first genetic evidence that UV radiation (UVR) may be the principal mutagen involved in BCC tumorigenesis. We review herein current advances in the understanding of the role of the HH pathway in BCC tumorigenesis including transgenic and knock-out animal models of HH pathway dysregulation. Furthermore, we summarize abnormalities in other tumor suppressors and oncogenes including ras and p53 and evidence for interactions between these regulatory genes and the HH pathway.

L11 ANSWER 22 OF 58 MEDLINE
ACCESSION NUMBER: 1999432239 MEDLINE
DOCUMENT NUMBER: 99432239 PubMed ID: 10500183
TITLE: Autoproteolysis in nucleoporin biogenesis.
AUTHOR: Rosenblum J S; Blobel G
CORPORATE SOURCE: Laboratory of Cell Biology, Rockefeller University, New York, NY 10021, USA.. rosenbj@rockvax.rockefeller.edu
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Sep 28) 96 (20) 11370-5. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991101
Last Updated on STN: 20000303
Entered Medline: 19991021

AB We have molecularly characterized a proteolytic cleavage in conserved nuclear pore complex proteins. This cleavage, previously demonstrated to be essential for the biogenesis of two nuclear pore complex proteins in mammals (Nup98 and Nup96) and yeast (Nup145-N and Nup145-C), occurs between Phe and Ser residues within a highly conserved domain in a polyprotein precursor. Here, we show that a protease is not involved in the cleavage event. By using a combination of domain mapping and site-directed **mutagenesis**, we demonstrate that the human nuclear pore complex protein Nup98 specifically cleaves itself between F863 and S864. A region of Nup98, amino acids 715-920, is able to cleave, whereas a smaller region, amino acids 772-920, does not cleave. In addition, we have generated a Nup98 mutant that cleaves under defined conditions in vitro. Further, the two cleaved fragments of Nup98 form a complex, providing a possible mechanism whereby specific, yet low-affinity, binding between Nup98 and Nup96 is responsible for the nuclear targeting of Nup96. Although apparently unrelated evolutionarily, Nup98 has converged on an autoproteolytic biogenesis mechanism similar to that of **hedgehog** proteins, the inteins, and the N-terminal nucleophile proteins.

L11 ANSWER 23 OF 58 MEDLINE
ACCESSION NUMBER: 1999406628 MEDLINE
DOCUMENT NUMBER: 99406628 PubMed ID: 10477300
TITLE: Proteolysis of cubitus interruptus in Drosophila requires phosphorylation by protein kinase A.
AUTHOR: Price M A; Kalderon D
CORPORATE SOURCE: Department of Biological Sciences, Columbia University, New York, New York 10027, USA.
CONTRACT NUMBER: GM41815 (NIGMS)
SOURCE: DEVELOPMENT, (1999 Oct) 126 (19) 4331-9. Journal code: ECW; 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991104

AB The **Hedgehog** signal transduction pathway is involved in diverse patterning events in many organisms. In Drosophila, **Hedgehog** signaling regulates transcription of target genes by modifying the activity of the DNA-binding protein Cubitus interruptus (Ci). **Hedgehog** signaling inhibits proteolytic cleavage of full-length Ci (Ci-155) to Ci-75, a form that represses some target genes, and also converts the full-length form to a potent transcriptional activator. Reduction of protein kinase A (PKA) activity also leads to accumulation of

full-length Ci and to ectopic expression of **Hedgehog** target genes, prompting the hypothesis that PKA might normally promote cleavage to Ci-75 by directly phosphorylating Ci-155. Here we show that a mutant form of Ci lacking five potential PKA phosphorylation sites (Ci5m) is not detectably cleaved to Ci-75 in Drosophila embryos. Moreover, changes in PKA activity dramatically altered levels of full-length wild-type Ci in embryos and imaginal discs, but did not significantly alter full-length Ci5m levels. We corroborate these results by showing that Ci5m is more active than wild-type Ci at inducing ectopic transcription of the Hh target gene wingless in embryos and that inhibition of PKA enhances induction of wingless by wild-type Ci but not by Ci5m. We therefore propose that PKA phosphorylation of Ci is required for the proteolysis of Ci-155 to Ci-75 in vivo. We also show that the activity of Ci5m remains **Hedgehog** responsive if expressed at low levels, providing further evidence that the full-length form of Ci undergoes a **Hedgehog** -dependent activation step.

L11 ANSWER 24 OF 58 MEDLINE
ACCESSION NUMBER: 1999350224 MEDLINE
DOCUMENT NUMBER: 99350224 PubMed ID: 10419691
TITLE: Constitutive activation of sonic **hedgehog** signaling in the chicken mutant talpid(2): Shh-independent outgrowth and polarizing activity.
AUTHOR: Caruccio N C; Martinez-Lopez A; Harris M; Dvorak L; Bitgood J; Simandl B K; Fallon J F
CORPORATE SOURCE: Department of Anatomy, University of Wisconsin at Madison, Madison, Wisconsin, 53706, USA.
CONTRACT NUMBER: HD32551 (NICHD)
T32GM07507 (NIGMS)
T32HD07477 (NICHD)
SOURCE: DEVELOPMENTAL BIOLOGY, (1999 Aug 1) 212 (1) 137-49.
Journal code: E7T; 0372762. ISSN: 0012-1606.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990910
Last Updated on STN: 19990910
Entered Medline: 19990824

AB We have examined the developmental properties of the polydactylous chicken mutant, talpid(2). Ptc, Gli1, Bmp2, Hoxd13, and Fgf4 are expressed throughout the anteroposterior axis of the mutant limb bud, despite normal Shh expression. The expression of Gli3, Ihh, and Dhh appears to be normal, suggesting that the Shh signaling pathway is constitutively active in talpid(2) mutants. We show that preaxial talpid(2) limb bud mesoderm has polarizing activity in the absence of detectable Shh mRNA. When the postaxial talpid(2) limb bud (including all Shh-expressing cells) is removed, the preaxial cells reform a normal-shaped talpid(2) limb bud (regulate). However, a Shh-expressing region (zone of polarizing activity) does not reform; nevertheless Fgf4 expression in the apical ectodermal ridge is maintained. Such reformed talpid(2) limb buds develop complete talpid(2) limbs. After similar treatment, normal limb buds downregulate Fgf4, the preaxial cells do not regulate, and a truncated anteroposterior deficient limb forms. In talpid(2) limbs, distal outgrowth is independent of Shh and correlates with Fgf4, but not Fgf8, expression by the apical ectodermal ridge. We propose a model for talpid(2) in which leaky activation of the Shh signaling pathway occurs in the absence of Shh ligand.

L11 ANSWER 25 OF 58 MEDLINE
ACCESSION NUMBER: 1999311847 MEDLINE
DOCUMENT NUMBER: 99311847 PubMed ID: 10385121

TITLE: The SIL gene is required for mouse embryonic axial development and left-right specification.

AUTHOR: Izraeli S; Lowe L A; Bertness V L; Good D J; Dorward D W; Kirsch I R; Kuehn M R

CORPORATE SOURCE: Genetics Department, Medicine Branch, National Cancer Institute, NIH, Bethesda, Maryland 20889-5105, USA.

SOURCE: NATURE, (1999 Jun 17) 399 (6737) 691-4.
Journal code: NSC; 0410462. ISSN: 0028-0836.

PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199907

ENTRY DATE: Entered STN: 19990715
Last Updated on STN: 19990715
Entered Medline: 19990707

AB The establishment of the main body axis and the determination of left-right asymmetry are fundamental aspects of vertebrate embryonic development. A link between these processes has been revealed by the frequent finding of midline defects in humans with left-right anomalies. This association is also seen in a number of mutations in mouse and zebrafish, and in experimentally manipulated Xenopus embryos. However, the severity of laterality defects accompanying abnormal midline development varies, and the molecular basis for this variation is unknown. Here we show that mouse embryos lacking the early-response gene SIL have axial midline defects, a block in midline Sonic **hedgehog** (Shh) signalling and randomized cardiac looping. Comparison with Shh mutant embryos, which have axial defects but normal cardiac looping, indicates that the consequences of abnormal midline development for left-right patterning depend on the time of onset, duration and severity of disruption of the normal asymmetric patterns of expression of nodal, lefty-2 and Pitx2.

L11 ANSWER 26 OF 58 MEDLINE

ACCESSION NUMBER: 1999270580 MEDLINE

DOCUMENT NUMBER: 99270580 PubMed ID: 10340755

TITLE: Msx1 is required for the induction of Patched by Sonic **hedgehog** in the mammalian tooth germ.

AUTHOR: Zhang Y; Zhao X; Hu Y; St Amand T; Zhang M; Ramamurthy R; Qiu M; Chen Y

CORPORATE SOURCE: Department of Cell and Molecular Biology, Tulane University, New Orleans, Louisiana 70118, USA.

SOURCE: DEVELOPMENTAL DYNAMICS, (1999 May) 215 (1) 45-53.
Journal code: A9U; 9201927. ISSN: 1058-8388.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199908

ENTRY DATE: Entered STN: 19990827
Last Updated on STN: 19990827
Entered Medline: 19990818

AB We have used the mouse developing tooth germ as a model system to explore the transmission of Sonic **hedgehog** (Shh) signal in the induction of Patched (Ptc). In the early developing molar tooth germ, Shh is expressed in the dental epithelium, and the transcripts of Shh downstream target genes Ptc and Gli1 are expressed in dental epithelium as well as adjacent mesenchymal tissue. The homeobox gene Msx1 is also expressed in the dental mesenchyme of the molar tooth germ at this time. We show here that the expression of Ptc, but not Gli1, was downregulated in the dental mesenchyme of Msx1 mutants. In wild-type E11.0 molar tooth mesenchyme SHH-soaked beads induced the expression of Ptc and Gli1. However, in Msx1 mutant dental mesenchyme SHH-soaked beads were able to induce Gli1 but failed to induce Ptc expression, indicating a requirement for Msx1 in the induction of Ptc by SHH. Moreover, we show that another signaling molecule, BMP4, was able to induce Ptc expression in wild-type dental mesenchyme, but induced a distinct expression pattern of Ptc in the Msx1 mutant molar mesenchyme. We conclude that in the context of the tooth germ

=> s hedgehog or patched

L1 5974 HEDGEHOG OR PATCHED

=> s dopa? or parkinson?

L2 256479 DOPA? OR PARKINSON?

=> s l1 and l2

L3 70 L1 AND L2

=> dup rem l3

PROCESSING COMPLETED FOR L3
L4 44 DUP REM L3 (26 DUPLICATES REMOVED)

=> d ibib abs 1-44

L4 ANSWER 1 OF 44 BIOTECHNO COPYRIGHT 2001 Elsevier Science B.V.
ACCESSION NUMBER: 2001:32480293 BIOTECHNO
TITLE: Of flies and men - Studying human disease in Drosophila
AUTHOR: Bernards A.; Hariharan I.K.
CORPORATE SOURCE: A. Bernards, Massachusetts Gen. Hosp. Cancer Ctr., Building 149, 13th Street, Charlestown, MA 02129, United States.
E-mail: abernard@helix.mgh.harvard.edu
SOURCE: Current Opinion in Genetics and Development, (01 JUN 2001), 11/3 (274-278), 49 reference(s)
CODEN: COGDET ISSN: 0959-437X
DOCUMENT TYPE: Journal; General Review
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2001:32480293 BIOTECHNO
AB During the past year, the Drosophila genome has been sequenced. More than
60% of genes implicated in human disease have Drosophila orthologues. Developments in RNA-mediated interference and homologous recombination have made 'reverse genetics' feasible in Drosophila. Conventional Drosophila genetics is being used increasingly to place human disease genes of unknown function in the context of functional pathways.

L4 ANSWER 2 OF 44 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001325503 MEDLINE
DOCUMENT NUMBER: 21213804 PubMed ID: 11312556
TITLE: Sonic **hedgehog** and FGF8: inadequate signals for the differentiation of a **dopamine** phenotype in mouse and human neurons in culture.
AUTHOR: Stull N D; Iacovitti L
CORPORATE SOURCE: Department of Neurology, Thomas Jefferson University Medical College, 1025 Walnut Street, Philadelphia, Pennsylvania, 19107, USA.
CONTRACT NUMBER: NS 32519 (NINDS)
NS24204 (NINDS)
SOURCE: EXPERIMENTAL NEUROLOGY, (2001 May) 169 (1) 36-43.
Journal code: EQF; 0370712. ISSN: 0014-4886.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: [redacted]ity Journals
ENTRY MONTH: 20[redacted]6
ENTRY DATE: Entered STN: 20010611
Last Updated on STN: 20010611
Entered PubMed: 20010423
Entered Medline: 20010607

AB Embryonic mouse striatal neurons and human neurons derived from the NT2/hNT stem cell line can be induced, in culture, to express the **dopaminergic** (DA) biosynthetic enzyme tyrosine hydroxylase (TH). The novel expression of TH in these cells is signaled by the synergistic interaction of factors present in the media, such as fibroblast growth factor 1 (FGF1) and one of several possible coactivators [DA, phorbol 12-myristate 13-acetate (TPA), isobutylmethylxanthine (IBMX), or forskolin]. Similarly, in vivo, it has recently been reported that the expression of TH in the developing midbrain is mediated by the synergy of FGF8 and the patterning molecule sonic **hedgehog** (Shh). In the present study, we examined whether the putative in vivo DA differentiation factors can similarly signal TH in our in vitro cell systems. We found that FGF8 and Shh induced TH expression in fewer than 2% of NT2/hNT cells and less than 5% of striatal neurons. The latter could be amplified to as much as 30% by increasing the concentration of growth factor 10-fold or by the addition of other competent coactivators (IBMX/forskolin, TPA, and DA). Additivity/inhibitor experiments indicated that FGF8 worked through traditional tyrosine kinase-initiated MAP/MEK signaling pathways. However, the Shh signal transduction cascade remained unclear. These data suggest that cues effective in vivo may be less successful in promoting the differentiation of a DA phenotype in mouse and human neurons in culture. Thus, our ability to generate DA neurons from different cell lines, for use in the treatment of **Parkinson**'s disease, will depend on the identification of appropriate differentiation signals for each cell type under investigation. Copyright 2001 Academic Press.

L4 ANSWER 3 OF 44 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2000129935 MEDLINE
DOCUMENT NUMBER: 20129935 PubMed ID: 10662651
TITLE: Control of chick tectum territory along dorsoventral axis by Sonic **hedgehog**.
AUTHOR: Watanabe Y; Nakamura H
CORPORATE SOURCE: Department of Molecular Neurobiology, Institute of Development, Aging and Cancer, Tohoku University, Aoba-ku, Sendai 980-8575, Japan.. yuji@idac.tohoku.ac.jp
SOURCE: DEVELOPMENT, (2000 Mar) 127 (5) 1131-40.
Journal code: ECW; 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000403

AB Chick midbrain comprises two major components along the dorsoventral axis, the tectum and the tegmentum. The alar plate differentiates into the optic tectum, while the basal plate gives rise to the tegmentum. It is largely unknown how the differences between these two structures are molecularly controlled during the midbrain development. The secreted protein Sonic **hedgehog** (Shh) produced in the notochord and floor plate induces differentiation of ventral cell types of the central nervous system. To evaluate the role of Shh in the establishment of dorsoventral polarity in the developing midbrain, we have ectopically expressed Shh unilaterally in the brain vesicles including whole midbrain of E1.5 chick embryos in ovo. Ectopic Shh repressed normal growth of the tectum, producing dorsally enlarged tegmentum region. In addition, the expression of several genes

crucial for tect[redacted]ormation was strongly suppres[redacted]in the midbrain and isthmus. Markers [redacted] midbrain roof plate were inh[redacted]ed, indicating that the roof plate was not fully generated. After E5, the tectum territory of Shh-transfected side was significantly reduced and was fused with that of untransfected side. Moreover, ectopic Shh induced a considerable number of SC1-positive motor neurons, overlapping markers such as HNF-3(beta) (floor plate), Isl-1 (postmitotic motor neuron) and Lim1/2. **Dopaminergic** and serotonergic neurons were also generated in the dorsally extended region. These changes indicate that ectopic Shh changed the fate of the mesencephalic alar plate to that of the basal plate, suppressing the massive cell proliferation that normally occurs in the developing tectum. Taken together our results suggest that Shh signaling restricts the tectum territory by controlling the molecular cascade for tectum formation along dorsoventral axis and by regulating neuronal cell diversity in the ventral midbrain.

L4 ANSWER 4 OF 44 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000291199 MEDLINE
DOCUMENT NUMBER: 20291199 PubMed ID: 10828249
TITLE: Electrogenic Na(+)/Ca(2+) exchange. A novel amplification step in squid olfactory transduction.
AUTHOR: Danaceau J P; Lucero M T
CORPORATE SOURCE: Interdepartmental Program in Neuroscience, School of Medicine, Salt Lake City, UT 84108, USA.
CONTRACT NUMBER: DC02587 (NIDCD)
SOURCE: JOURNAL OF GENERAL PHYSIOLOGY, (2000 Jun) 115 (6) 759-68.
Journal code: I8N; 2985110R. ISSN: 0022-1295.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000810
Last Updated on STN: 20000810
Entered Medline: 20000721

AB Olfactory receptor neurons (ORNs) from the squid, Lolliguncula brevis, respond to the odors l-glutamate or **dopamine** with increases in internal Ca(2+) concentrations ([Ca(2+)](i)). To directly asses the effects of increasing [Ca(2+)](i) in perforated-**patched** squid ORNs, we applied 10 mM caffeine to release Ca(2+) from internal stores. We observed an inward current response to caffeine. Monovalent cation replacement of Na(+) from the external bath solution completely and selectively inhibited the caffeine-induced response, and ruled out the possibility of a Ca(2+)-dependent nonselective cation current. The strict dependence on internal Ca(2+) and external Na(+) indicated that the inward current was due to an electrogenic Na(+)/Ca(2+) exchanger. Block of the caffeine-induced current by an inhibitor of Na(+)/Ca(2+) exchange (50-100 microM 2',4'-dichlorobenzamil) and reversibility of the exchanger current, further confirmed its presence. We tested whether Na(+)/Ca(2+) exchange contributed to odor responses by applying the aquatic odor l-glutamate in the presence and absence of 2', 4'-dichlorobenzamil. We found that electrogenic Na(+)/Ca(2+) exchange was responsible for approximately 26% of the total current associated with glutamate-induced odor responses. Although Na(+)/Ca(2+) exchangers are known to be present in ORNs from numerous species, this is the first work to demonstrate amplifying contributions of the exchanger current to odor transduction.

L4 ANSWER 5 OF 44 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000508967 MEDLINE
DOCUMENT NUMBER: 20513610 PubMed ID: 11061432
TITLE: Genetic and epigenetic control of midbrain

do[redacted]ergic neuron development.
AUTHOR: Per[redacted]one-Capano C; Di Porzio U
CORPORATE SOURCE: Istituto Internazionale di Genetica e Biofisica, CNR, Naples, Italy.
SOURCE: INTERNATIONAL JOURNAL OF DEVELOPMENTAL BIOLOGY, (2000) 44 (6 Spec No) 679-87. Ref: 72
Journal code: AV3; 8917470. ISSN: 0214-6282.
PUB. COUNTRY: Spain
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered PubMed: 20010205
Entered Medline: 20010329

AB The relatively few **dopaminergic** (DA) neurons in the mammalian brain regulate many important neural functions, including motor integration, neuroendocrine hormone release, cognition, emotive behaviors and reward. A number of laboratories, including ours, have contributed to unravel the mechanisms of DA phenotype induction and maturation and elucidated the role of epigenetic factors involved in specification, development and maintenance of midbrain **dopaminergic** functions. DA progenitors are first "committed" to give rise to DA neurons by the action of two secreted factors, Sonic **hedgehog** and fibroblast growth factor 8 (FGF8). Subsequently, the function of selectively activated transcription factors, Nurr1 and Ptx3, is required for the DA final determination. Further development of DA neurotransmission requires specific interactions with the developing target striatal cells, which modulate key DA functions, namely synthesis and uptake of the neurotransmitter. Committed and determined DA neurons express the key genes involved in DA neurotransmission at different times in development. In rodents, synthesis and intracellular accumulation of DA is achieved shortly after expression of Nurr1, while the onset of high affinity uptake, responsible for ending the neurotransmission, takes place after a few days. Cell contacts between the presynaptic DA neurons and target striatal neurons are apparently necessary for the fine modulation of DA function, in vivo and in vitro. Strikingly, the in situ maturation and phenotypic specialization of DA neurons grafted into the adult striatum/caudate-putamen parallels the normal development of committed fetal **dopamine** neurons during neurogenesis. The correct matching between the right presynaptic and postsynaptic neurons is required also for grafted DA cells.

L4 ANSWER 6 OF 44 MEDLINE
ACCESSION NUMBER: 2000456126 MEDLINE
DOCUMENT NUMBER: 20296936 PubMed ID: 10835609
TITLE: Efficient generation of midbrain and hindbrain neurons from
mouse embryonic stem cells.
AUTHOR: Lee S H; Lumelsky N; Studer L; Auerbach J M; McKay R D
CORPORATE SOURCE: Laboratory of Molecular Biology, NINDS, NIH, Bethesda, MD 20892, USA.
SOURCE: NATURE BIOTECHNOLOGY, (2000 Jun) 18 (6) 675-9.
Journal code: CQ3; 9604648. ISSN: 1087-0156.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001005
Last Updated on STN: 20001005
Entered Medline: 20000925

AB Embryonic stem (ES) cells are clonal cell lines derived from the inner cell mass of the developing blastocyst that can proliferate extensively in
vitro and are capable of adopting all the cell fates in a developing

embryo. Clinical interest in the use of ES cells has been stimulated by studies showing that isolated human cells with ES properties from the inner cell mass or developing germ cells can provide a source of somatic precursors. Previous studies have defined in vitro conditions for promoting the development of specific somatic fates, specifically, hematopoietic, mesodermal, and neurectodermal. In this study, we present a method for obtaining **dopaminergic** (DA) and serotonergic neurons in high yield from mouse ES cells in vitro. Furthermore, we demonstrate that the ES cells can be obtained in unlimited numbers and that these neuron types are generated efficiently. We generated CNS progenitor populations from ES cells, expanded these cells and promoted their differentiation into **dopaminergic** and serotonergic neurons in the presence of mitogen and specific signaling molecules. The differentiation and maturation of neuronal cells was completed after mitogen withdrawal from the growth medium. This experimental system provides a powerful tool for analyzing the molecular mechanisms controlling the functions of these neurons in vitro and in vivo, and potentially for understanding and treating neurodegenerative and psychiatric diseases.

L4 ANSWER 7 OF 44 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2000456743 MEDLINE
DOCUMENT NUMBER: 20309214 PubMed ID: 10852374
TITLE: Holoprosencephaly, sacral anomalies, and situs ambiguus in an infant with partial monosomy 7q/trisomy 2p and SHH and HLXB9 haploinsufficiency..
AUTHOR: Nowaczyk M J; Huggins M J; Tomkins D J; Rossi E; Ramsay J A; Woulfe J; Scherer S W; Belloni E
CORPORATE SOURCE: Department of Pathology and Molecular Medicine, Hamilton Health Sciences Corporation and McMaster University, Canada.. nowaczyk@hhsc.ca
SOURCE: CLINICAL GENETICS, (2000 May) 57 (5) 388-93.
Journal code: DDT; 0253664. ISSN: 0009-9163.
PUB. COUNTRY: Denmark
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001005
Last Updated on STN: 20001005
Entered Medline: 20000928

AB We report an infant with holoprosencephaly (HPE), sacral anomalies, and situs ambiguus with a 46,XY,der(7)t(2;7)(p23.2;q36.1) karyotype as a result of an adjacent-1 segregation of a t(2;7)pat. The chromosomal abnormality was diagnosed prenatally after sonographic detection of HPE in the fetus. The baby was born at 37 weeks gestation, and died in the newborn period; he had dysmorphic features consistent with HPE sequence. Postmortem internal evaluation showed semilobar HPE, abdominal situs ambiguus, multiple segments of bowel atresia, dilatation of the ureters, and bony sacral anomalies. Molecular analysis confirmed hemizygosity for the SHH and HLXB9 genes, which are likely to be responsible for the HPE and sacral phenotypes, respectively. Immunohistochemical studies showed intact **dopaminergic** pathways in the mesencephalon, suggesting that midbrain **dopamine** neuron induction appears to require only one functioning SHH allele.

L4 ANSWER 8 OF 44 BIOTECHNO COPYRIGHT 2001 Elsevier Science B.V.
ACCESSION NUMBER: 2000:30311725 BIOTECHNO
TITLE: Applications of developmental biology to medicine and animal agriculture
AUTHOR: Smith R.C.; Rhodes S.J.
CORPORATE SOURCE: Dr. R.C. Smith, Department of Biology, IUPUI, 723 W. Michigan Street, Indianapolis, IN 46202-5132, United States.
SOURCE: Progress in Drug Research, (2000), 54/- (213-256), 221
reference(s)

CODEN: FAZMAE ISSN: 0071-786[redacted]
DOCUMENT TYPE: Journal; General Review
COUNTRY: Switzerland
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2000:30311725 BIOTECHNO
AB With the complete sequence of the human genome expected by winter 2001, genomic-based drug discovery efforts of the pharmaceutical industry are focusing on finding the relatively few therapeutically useful genes from among the total gene set. Methods to rapidly elucidate gene function will have increasing value in these investigations. The use of model organisms in functional genomics has begun to be recognized and exploited and is one example of the emerging use of the tools of developmental biology in recent drug discovery efforts. The use of protein products expressed during embryogenesis and the use of certain pluripotent cell populations (stem cells) as candidate therapeutics are other applications of developmental biology to the treatment of human diseases. These agents may be used to repair damaged or diseased tissues by inducing or directing developmental programs that recapitulate embryonic processes to replace specialized cells. The activation or silencing of embryonic genes in the disease state, particularly those encoding transcription factors, is another avenue of exploitation. Finally, the direct drug-induced manipulation of embryonic development is a unique application of developmental biology in animal agriculture.

L4 ANSWER 9 OF 44 BIOTECHNO COPYRIGHT 2001 Elsevier Science B.V.
ACCESSION NUMBER: 2000:30810915 BIOTECHNO
TITLE: The decade of the brain: A brief review
AUTHOR: Tandon P.N.
CORPORATE SOURCE: Dr. P.N. Tandon, Department of Neurosurgery, All India Inst. of Medical Sciences, Neuroscience Centre, New Delhi 110029, India.
SOURCE: Neurology India, (2000), 48/3 (199-207), 99 reference(s)
CODEN: NURYAY ISSN: 0028-3886
DOCUMENT TYPE: Journal; General Review
COUNTRY: India
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2000:30810915 BIOTECHNO
AB Recognising the huge burden of neurological and psychiatric disorders and prompted by the potentials of new techniques of molecular biology, biotechnology, genetics and imaging to study these, the 1990s were declared the 'decade of the brain'. This stimulated global scientific efforts to understand the human brain in health and disease. This review summarises some of the major research achievements during the decade. While it is impossible to provide a comprehensive summary of the voluminous data that has been generated, it was decided to provided a bird's eye view of the recent advances in the fields of developmental neurobiology, neurogenetics, neurochemistry and imaging of the brain, which have direct relevance for the clinicians.

L4 ANSWER 10 OF 44 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2000118828 MEDLINE
DOCUMENT NUMBER: 20118828 PubMed ID: 10654667
TITLE: Epigenetic cues in midbrain **dopaminergic** neuron development.
AUTHOR: Perrone-Capano C; Da Pozzo P; di Porzio U
CORPORATE SOURCE: Istituto Internazionale di Genetica e Biofisica, CNR, Naples, Italy.. perrone@iigbna.iigb.na.cnr.it
SOURCE: NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS, (2000 Jan) 24 (1) 119-24.
Journal code: OA7; 7806090. ISSN: 0149-7634.

PUB. COUNTRY: [redacted]d States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20000229
Entered Medline: 20000217

AB Midbrain **dopaminergic** (DA) neurons subserve complex and varied neural functions in vertebrate CNS. Their progenitors give rise to DA neurons by the action of two extracellular inducers, Sonic **Hedgehog** and FGF8. After this first commitment, the function of selectively activated transcription factors, like the orphan steroid nuclear receptor Nurr1, is required for DA final determination. Subsequently, DA function is selectively modulated by specific interaction with the developing striatal target tissue. Committed and determined DA neurons express the key genes involved in DA neurotransmission at different times in development. Synthesis and intracellular accumulation of DA is achieved shortly after expression of Nurr1, while high affinity uptake, responsible for ending the neurotransmission, takes place after a few days. Cell contacts between the presynaptic DA neurons and target striatal neurons are apparently necessary for the fine modulation of DA function, in vivo and in vitro.

L4 ANSWER 11 OF 44 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:223110 BIOSIS
DOCUMENT NUMBER: PREV200000223110
TITLE: Sonic **Hedgehog** attenuates behavioral and anatomical deficits induced by 6-hydroxydopamine in rats.
AUTHOR(S): Shults, Clifford W. (1); Tsuboi, Kyoko (1); Kimber, Teresa A. (1)
CORPORATE SOURCE: (1) La Jolla, CA USA
SOURCE: Neurology, (April 11, 2000) Vol. 54, No. 7 Supp. 3, pp. A53.
Meeting Info.: 52nd Annual Meeting of the American Academy of Neurology. San Diego, CA, USA April 29-May 06, 2000 American Academy of Neurology
. ISSN: 0028-3878.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L4 ANSWER 12 OF 44 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2000075285 MEDLINE
DOCUMENT NUMBER: 20075285 PubMed ID: 10607393
TITLE: The seven-transmembrane receptor smoothened cell-autonomously induces multiple ventral cell types.
AUTHOR: Hynes M; Ye W; Wang K; Stone D; Murone M; Sauvage F d; Rosenthal A
CORPORATE SOURCE: Department of Neuroscience, Genentech, Inc., South San Francisco, California 94080, USA.. mah@gene.com
SOURCE: NATURE NEUROSCIENCE, (2000 Jan) 3 (1) 41-6.
Journal code: DA8; 9809671. ISSN: 1097-6256.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000124

AB Sonic **Hedgehog** (Shh) is a secreted protein that controls cell fate and mitogenesis in the developing nervous system. Here we show that a constitutively active form of Smoothened (Smo-M2) mimics concentration-dependent actions of Shh in the developing neural tube, including activation of ventral marker genes (HNF3beta, **patched**, Nkx2.2, netrin-1), suppression of dorsal markers (Pax-3, Gli-3, Ephrin A5)

and induction of [redacted]tral neurons (**dopaminergic**, [redacted]otonergic) and ventrolateral motor neurons (Islet-1+, Islet[redacted]/HB9+) and interneurons (Engrailed-1+, CHX10+). Furthermore, Smo-M2's patterning activities were cell autonomous, occurring exclusively in cells expressing Smo-M2. These findings suggest that Smo is a key signaling component in the Hh receptor and that Shh patterns the vertebrate nervous system as a morphogen, rather than through secondary relay signals.

L4 ANSWER 13 OF 44 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:88086 BIOSIS
DOCUMENT NUMBER: PREV200100088086
TITLE: Human neural stem cells transfected with Nurr1 gene express **dopaminergic** phenotype.
AUTHOR(S): Lee, M. A. (1); Lee, H. S.; Jung, S. H.; Park, S. Y.; Huh, S. O.; Ryu, J. K.; Kim, H. J.; Jin, B. K.; Ichinose, H.; Kim, S. U.
CORPORATE SOURCE: (1) Ajou University, Suwon South Korea
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-313.7. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Neural stem cells(NSCs) of the CNS have recently aroused a great deal of interest not only because of their importance in basic neural development but also their therapeutic potential for neurological diseases such as **Parkinson** disease and stroke. During the CNS development, specification of midbrain DA system is determined by two molecular cascades.In one pathway,FGF-8,sonic **hedgehog** and transcription factor Nurr1 specify DA neurotransmitter phenotype, and in the another, transcription factors Lmx1b and Ptx3 are important. In Nurr1 knock-out mouse, TH positive cells fail to appear in substantia nigra, indicating that Nurr1 is essential in specification of DA phenotype. In this study, we used immortalized human NSCs retrovirally transduced with Nurr1 gene to probe the Nurr1-mediated mechanism to induce DA phenotype. While Nurr1 overexpression alone did not generate DA phenotype in NSCs, application of retinoid and foskolin induced expression of TH and AADC mRNAs. In addition, co-cultures of Nurr1 expressing NSCs with human astrocytes induced a marked increase of TH expression. In this co-culture system, addition of retinoids and foskolin dramatically increased expression of TH. These results indicate that the immortalized human NSCs with Nurr1 gene have the clinical utility for cell replacement for patients suffering from **Parkinson** disease(supported by KOSEF)

L4 ANSWER 14 OF 44 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:88175 BIOSIS
DOCUMENT NUMBER: PREV200100088175
TITLE: Cooperative effects of sonic **hedgehog** and NGF on basal forebrain cholinergic neurons in vitro.
AUTHOR(S): Reilly, J. O. (1); Mahanthappa, N. K.; Allendoerfer, K. L.
CORPORATE SOURCE: (1) Ontogeny, Inc., Cambridge, MA USA
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-319.9. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Sonic **hedgehog** (Shh) is a secreted protein that acts as an

inducing molecul[redacted]rly in the development of the [redacted]ntral neuraxis. Shh mediates the specification of several neural popu[redacted]ions including spinal motor neurons, **dopaminergic** neurons, and cholinergic neurons during embryonic development. Since the Shh receptor **patched**-1 (Ptc-1) is also expressed by basal forebrain cholinergic neurons in early postnatal and adult life, we asked whether these neurons can respond to exogenously added Shh in vitro. We added Shh alone and in combination with

other growth factors to cultures derived from embryonic day 16 rat basal forebrain. We find that Shh treatment alone has no effect, but that Shh synergizes with nerve growth factor (NGF), increasing the number of choline acetyltransferase (ChAT) positive cells by four-fold over the untreated cultures and two-fold over NGF alone. Using 3H-thymidine incorporation combined with ChAT immunohistochemistry, we find that this synergistic effect does not appear to be the result of enhanced proliferation of early cholinergic precursors. Given the previous reports of the role of Shh in differentiation of neurons, it is hypothesized that the effects observed are due to increased differentiation or survival of cholinergic neurons in these cultures in response to Shh and NGF. These experiments imply a role for Shh in mature cells and suggests a therapeutic value for Shh in neurodegenerative disease.

L4 ANSWER 15 OF 44 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:93450 BIOSIS
DOCUMENT NUMBER: PREV200100093450
TITLE: Molecular control of **dopaminergic** differentiation in bFGF expanded midbrain precursors.
AUTHOR(S): Studer, L. (1); Lee, S. H.; Panchision, D.; Pickel, J.; McKay, R. D.
CORPORATE SOURCE: (1) MSKCC, New York, NY USA
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-504.9. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In vitro proliferation of CNS precursors is a promising cell source for brain repair. We recently demonstrated 1 that rat mesencephalic precursor cells can be expanded in vitro with bFGF and converted into functional **dopaminergic** neurons that, upon transplantation, alleviate behavioral symptoms in **Parkinsonian** rats. The efficiency of the system has been limited to a 10-100 fold in vitro increase of total cell numbers. Expansion of precursors for longer in vitro periods results in a dramatically reduced **dopaminergic** yield despite intact neuronal differentiation. We identified several genes that are differentially expressed in precursors expanded for various in vitro periods that correlate with the ability of the cells to generate **dopaminergic** neurons. Long-term expanded precursors showed decreased expression levels of sonic **hedgehog**, FGF8 and Nurr1 as well as a loss of Pax2, Pax5 and Pax8 expression by RT-PCR. Re-introduction of some of these differentially expressed genes into long-term expanded precursors partially restored TH differentiation. Our study provides a powerful technique to identify genes involved in the regional commitment of CNS precursor cells and to develop rational strategies for the ex-vivo generation of specific neurons for brain repair. (L. Studer, V. Tabar, R. D. McKay, Nature Neurosci. 1, 290-295 (1998))

L4 ANSWER 16 OF 44 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:120680 BIOSIS
DOCUMENT NUMBER: PREV200100120680
TITLE: Adenovirus-mediated gene transfer of Shh, Gli-1 and Nurr1 in a rat model of **Parkinson**'s disease.
AUTHOR(S): Hurtado-Lorenzo, A.; Millan, E.; Castro, M.; Lowenstein, P.
R.
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No.

[redacted]pp. Abstract No.-666.17. prin[redacted]
Meeting Info.: 30th Annual Meeting [redacted] the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Several lines of evidence demonstrate the feasibility of adenoviral gene therapy for **Parkinson**'s disease. Recently it has been demonstrated that Sonic **hedgehog** (Shh) is a neurotrophic and neuroprotective factor for **Dopaminergic** neurones (DA) in vitro. Increasing evidence suggests that the Shh signal is mediated by the regulation of Gli-1 expression. As an approach to directly regulate, at the transcriptional level, the neuroprotective signal of Shh, a recombinant adenovirus (RAd) expressing human Gli-1 has been constructed. An adenovirus expressing the transcription factor Nurr1, a crucial gene for differentiation and survival of DA was also generated. In this study we demonstrate that a RAd encoding Shh is able to protect ventral mesencephalic neurones from the toxic insult of the neurotoxin 6-OHDA, in vitro. In order to test whether Shh, Gli-1 or Nurr-1 are able to protectin vivo against this neurotoxin, Sprague-Dawley rats were intrastriatally injected with a dose of 3.2x107 pfu/3mul of RAdShh, RAdGli-1 or RAdNurr1 together with the retrograde tracer Fluorogold (FG). One week after, degeneration of the nigro-striatal pathway was induced by injecting 6-OHDA at the same coordinates used for the vectors and FG. The rats were sacrificed 6 weeks after the injection of 6-OHDA. The results demonstrate that neither RAdShh nor RAdGli-1 or RAdNurr1 were able to induce a significant protection against the toxic insult of 6-OHDA. These data indicate that in this particular in vivo model and at the dose of RAd used, gene transfer of Shh, Gli-1 and Nurr1 is unable to elicit neuroprotective effects in the substantia nigra.

L4 ANSWER 17 OF 44 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:109696 BIOSIS
DOCUMENT NUMBER: PREV200100109696
TITLE: Intrastriatal injection of sonic **hedgehog** reduces behavioral impairment in rat model of **Parkinson**'s disease.
AUTHOR(S): Tsuboi, K. (1); Shults, C. W.
CORPORATE SOURCE: (1) UC San Diego, La Jolla, CA USA
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-765.17. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Sonic **hedgehog** (Shh), a member of **hedgehog** family of signaling molecules, is necessary for normal axial patterning and cellular differentiation in the developing central nervous system. It is also known that Shh promotes the survival of fetal **dopaminergic** (DA) neurons and protects cultures of fetal midbrain DA neurons from the toxin effects of MPP+, a neurotoxin that induces **Parkinsonism** in vivo. In this study we examined the behavioral and anatomical effects of intrastriatal injection of singly myristoylated wild type human Shh N-terminal fragment (Shh-M) in a rat model of **Parkinson**'s disease. Five groups of rats received a series of injections of Shh-M (180 ng, 540 ng, 4.275 mug/injection), glial cell line-derived neurotrophic factor (GDNF) (1 mug/injection) or vehicle on days 1, 3, 5 and 8. On day 4, the animals received an intrastriatal injection of 15 mug 6-hydroxydopamine. Both Shh-M (180 ng/injection) and GDNF resulted in a

similar level [redacted] attenuation of drug-induced rotation. However, the area of preserved ty[redacted]ne hydroxylase immunoreactive [redacted]H-IR) fibers around injection site was larger in the GDNF-treated group than in the Shh-M(180 ng)-treated group. Furthermore, there were no significant differences in the density of TH-IR fibers around the injection site and in the preservation of nigral TH-IR neurons between the Shh-M-treated group and the vehicle-treated group, while the GDNF-treated group showed significantly higher density of TH-IR fibers and preservation of nigral TH-IR neurons. The behavioral effect of Shh-M may have been mediated by actions on the striatal neurons as well as on nigrostriatal DA system.

L4 ANSWER 18 OF 44 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:120682 BIOSIS
DOCUMENT NUMBER: PREV200100120682
TITLE: Effect of sonic **hedgehog** in the MPTP treated common marmoset.
AUTHOR(S): Dass, B.; Iravani, M. M.; Engber, T. M.; Galdes, A.; Jenner, P.
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-666.19. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Current treatments for **Parkinson**'s Disease (PD) fail to address the problem of ongoing degeneration of the nigrostriatal **dopaminergic** neurons. Sonic **hedgehog** (SHH) in vitro, has trophic effects on **dopaminergic** cell cultures, and protect these cells from MPTP toxicity. This would suggest that SHH might have potential as a therapy for PD. In this study, 0.1 and 1.0 ul SHH or vehicle was injected unilaterally on two occasions, 5 weeks apart, into the supra-nigral region of 17 MPTP treated common marmosets, in a blind fashion. Low dose SHH (0.1ug, n=5) produced a non-significant improvement in motor function and locomotor activity following the first administration of SHH. Following the second administration of SHH, locomotor scores were lowered by 15% from control. Motor disability (29%) and locomotor activity (28%) were significantly improved following the first injection of high dose (1ug, n=6) SHH, but this improvement was not maintained following the second dose. Locomotor activity returned to control levels following the second administration of SHH in the group receiving high dose SHH, whilst motor disability increased 11%. Control animals (n=6), injected with 1ul of 0.1M PBS, showed no significant changes in locomotor activity. Compared to the contralateral substantia nigra, the ipsilateral SN exhibited a greater density of tyrosine hydroxylase +ve neurons in animals receiving SHH compared to control animals. Animals receiving a low dose of SHH showed a 21% non significant increase, whilst with high dose SHH, animals showed a 57% significant increase. The results indicate that SHH may have potential therapeutic effects for the treatment of PD.

L4 ANSWER 19 OF 44 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1999387970 MEDLINE
DOCUMENT NUMBER: 99387970 PubMed ID: 10457011
TITLE: Nurr1, an orphan nuclear receptor, is a transcriptional activator of endogenous tyrosine hydroxylase in neural progenitor cells derived from the adult brain.
AUTHOR: Sakurada K; Ohshima-Sakurada M; Palmer T D; Gage F H
CORPORATE SOURCE: Laboratory of Genetics, The Salk Institute for Biological Studies, La Jolla, California 92037, USA.
CONTRACT NUMBER: AG06088 (NIA)
NO1-NS-6-2348 (NINDS)
SOURCE: DEVELOPMENT, (1999 Sep) 126 (18) 4017-26.
Journal code: ECW; 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991101
Last Updated on STN: 19991101
Entered Medline: 19991021

AB Adult rat-derived hippocampal progenitor cells express many of the molecules implicated in midbrain **dopaminergic** determination, including FGF receptors 1, 2 and 3, the sonic **hedgehog** receptor components Smo and Ptc, and the region-specific transcription factors Ptx3
and Nurr1. Here we use undifferentiated progenitors to probe the events leading to the **dopaminergic** phenotype and find that the influences of Nurr1 can be temporally and mechanistically uncoupled from the patterning influences of sonic **hedgehog** and FGF-8 or the more generic process of neuronal differentiation itself. In gain-of-function experiments, Nurr1 is able to activate transcription of the tyrosine hydroxylase gene by binding a response element within a region of the tyrosine hydroxylase promoter necessary for midbrain-specific expression. This activation is mediated through a retinoid X receptor independent mechanism and occurs in all precursors, regardless of differentiation status. Overexpression of Nurr1 does not affect proliferation or stimulate neuronal differentiation and has no influence on the expression of other **dopaminergic** markers. This uncoupling of tyrosine hydroxylase expression from other **dopaminergic** markers suggests that the midbrain **dopaminergic** identity is dictated by a combination of pan-**dopaminergic** (e.g., Shh/FGF-8) and region-specific (Nurr1) mechanisms.

L4 ANSWER 20 OF 44 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:135122 BIOSIS
DOCUMENT NUMBER: PREV200000135122
TITLE: Sonic **hedgehog** and FGF8: Inadequate signals for the differentiation of a **dopamine** phenotype in culture.
AUTHOR(S): Stull, N. D. (1); Iacovitti, L. (1)
CORPORATE SOURCE: (1) Department of Neurology, Thomas Jefferson University Medical College, Philadelphia, PA, 19107 USA
SOURCE: Society for Neuroscience Abstracts., (1999) Vol. 25, No. 1-2, pp. 1030.
Meeting Info.: 29th Annual Meeting of the Society for Neuroscience. Miami Beach, Florida, USA October 23-28, 1999
Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L4 ANSWER 21 OF 44 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:67205 BIOSIS
DOCUMENT NUMBER: PREV200000067205
TITLE: Induction of rat midbrain **dopaminergic** neurons in vitro by Sonic **Hedgehog** and modulation of Nurr1 gene expression.
AUTHOR(S): Da Pozzo, P. (1); Perrone-Capano, C. (1); di Porzio, U. (1)
CORPORATE SOURCE: (1) International Institute of Genetics and Biophysics, CNR, Via Marconi 10, 80125, Naples Italy
SOURCE: Society for Neuroscience Abstracts, (1999) Vol. 25, No. 1-2, pp. 252.
Meeting Info.: 29th Annual Meeting of the Society for Neuroscience, Part 1 Miami Beach, Florida, USA October 23-28, 1999 The Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 22 OF 44 [redacted]LINE DUPLICATE 9
ACCESSION NUMBER: 1999143423 MEDLINE
DOCUMENT NUMBER: 99143423 PubMed ID: 9988878
TITLE: Effects of prenatal cocaine exposure on embryonic expression of sonic **hedgehog**.
AUTHOR: Koebbe M J; Golden J A; Bennett G; Finnell R H; Mackler S A
CORPORATE SOURCE: Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia 19104, USA.
CONTRACT NUMBER: NIDA 00199 (NIDA)
NIDA 07241 (NIDA)
SOURCE: TERATOLOGY, (1999 Jan) 59 (1) 12-9.
Journal code: VM8; 0153257. ISSN: 0040-3709.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990420
Last Updated on STN: 19990420
Entered Medline: 19990402

AB Cocaine use by pregnant women may adversely affect development and behavior in the exposed infants. Sonic **hedgehog** (shh) is a secreted protein that induces development of many structures in the embryo, including **dopaminergic** cells in the ventral midbrain, the limb buds, and eyes. Because prenatal cocaine exposure has been shown to adversely affect the morphogenesis of these and other systems, the present study was undertaken to test the hypothesis that maternal cocaine treatment would alter shh mRNA expression. Cocaine HCl (60 mg/kg i.p.) was administered to pregnant mice on gestational days 6-8, the time that immediately precedes the appearance of shh. Control dams received i.p. saline. Embryos from gestational days 9-11 were examined by in situ hybridization. The temporal and spatial patterns of shh expression were indistinguishable between embryos from cocaine- and saline-treated dams. Examination of forebrain, midbrain, and midbody spinal cord coronal sections failed to reveal any differences in the dorsoventral and mediolateral localization of shh. The distribution of mRNA for **patched** (ptc), the membrane receptor for shh, was also indistinguishable between both groups. Chick embryos were next used to examine the direct application of cocaine into the developing brain. Shh distribution was similarly unaffected in these chick embryos. These data show that maternal cocaine treatment during early neural tube development does not significantly alter the expression patterns of shh or ptc mRNA. Thus, congenital defects and behavioral abnormalities associated with maternal cocaine use do not appear to result from altered expression of the shh-ptc pathway.

L4 ANSWER 23 OF 44 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1999115779 MEDLINE
DOCUMENT NUMBER: 99115779 PubMed ID: 9914262
TITLE: Cultured insect mushroom body neurons express functional receptors for acetylcholine, GABA, glutamate, octopamine, and **dopamine**.
AUTHOR: Cayre M; Buckingham S D; Yagodin S; Sattelle D B
CORPORATE SOURCE: Babraham Institute Laboratory of Molecular Signalling, Department of Zoology, University of Cambridge, Cambridge CB2 3EJ, United Kingdom.
SOURCE: JOURNAL OF NEUROPHYSIOLOGY, (1999 Jan) 81 (1) 1-14.
Journal code: JC7; 0375404. ISSN: 0022-3077.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990402
Last Updated on STN: 19990402
Entered Medline: 19990322

AB Fluorescence ca[redacted] imaging with fura-2 and whol[redacted]cell, patch-clamp electrophysiology, was applied to cultured Kenyon [redacted]ls (interneurons) isolated from the mushroom bodies of adult crickets (Acheta domesticus) to demonstrate the presence of functional neurotransmitter receptors. In all cells investigated, 5 microM acetylcholine (ACh, n = 52) evoked an increase in intracellular free calcium ([Ca2+]i). Similar effects were observed in response to 10 microM nicotine. The ACh response was insensitive to atropine (50 microM) but was reduced by mecamylamine (50 microM) and alpha-bungarotoxin (alpha-bgt, 10 microM). ACh-induced inward ion currents (n = 28, EACh approximately 0 mV) were also blocked by 1 microM mecamylamine and by 1 microM alpha-bgt. Nicotine-induced inward currents desensitized more rapidly than ACh responses. Thus functional alpha-bgt-sensitive nicotinic ACh receptors are abundant on all Kenyon cells tested, and their activation leads to an increase in [Ca2+]i. gamma-Aminobutyric acid (GABA, 100 microM) triggered a sustained decrease in [Ca2+]i. Similar responses were seen with a GABAA agonist, muscimol (100 microM), and a GABAB agonist, 3-APPA (1 mM), suggesting that more than one type of GABA receptor can affect [Ca2+]i. This action of GABA was not observed when the extracellular KCl concentration was lowered. All cells tested (n = 26) with patch-clamp electrophysiology showed picrotoxinin (PTX)-sensitive, GABA-induced (30-100 microM) currents with a chloride-sensitive reversal potential. Thus, an ionotropic PTX-sensitive GABA receptor was found on all Kenyon cells tested. Most (61%) of the 54 cells studied responded to -glutamate (100 microM) application either with a biphasic increase in [Ca2+]i or with a single, delayed, sustained [Ca2+]i increase. Nearly all cells tested (95%, n = 19) responded to (100 microM) -glutamate with rapidly desensitizing, inward currents that reversed at approximately -30 mV. **Dopamine** (100 microM) elicited either a rapid or a delayed increase in [Ca2+]i in 63% of the 26 cells tested. The time course of these responses varied greatly among cells. **Dopamine** failed to elicit currents in patch-clamped cells (n = 4). A brief decrease in [Ca2+]i was induced by octopamine (100 microM) in approximately 54% of the cells tested (n = 35). However, when extracellular CaCl2 was lowered, octopamine triggered a substantial increase in [Ca2+]i in 35% of the cells tested (n = 26). No octopamine-elicited currents were detected in **patched**-clamped cells (n = 10).

L4 ANSWER 24 OF 44 MEDLINE DUPLICATE 11

ACCESSION NUMBER: 1998414555 MEDLINE
DOCUMENT NUMBER: 98414555 PubMed ID: 9742154
TITLE: Spinal cord neuronal precursors generate multiple neuronal phenotypes in culture.
AUTHOR: Kalyani A J; Piper D; Mujtaba T; Lucero M T; Rao M S
CORPORATE SOURCE: Department of Neurobiology and Anatomy, University of Utah School of Medicine, Salt Lake City, Utah 84132, USA.
CONTRACT NUMBER: NO1-HD-7-3263 (NICHD)
SOURCE: JOURNAL OF NEUROSCIENCE, (1998 Oct 1) 18 (19) 7856-68. Journal code: JDF; 8102140. ISSN: 0270-6474.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981021
Last Updated on STN: 19981021
Entered Medline: 19981009

AB Neuronal restricted precursors (NRPs) () can generate multiple neurotransmitter phenotypes during maturation in culture. Undifferentiated E-NCAM+ (embryonic neural cell adhesion molecule) immunoreactive NRPs are mitotically active and electrically immature, and they express only a subset of neuronal markers. Fully mature cells are postmitotic, process-bearing cells that are neurofilament-M and synaptophysin immunoreactive, and they synthesize and respond to different subsets of

neurotransmitte[redacted]ecules. Mature neurons that [redacted]thesize and respond to glycine, glutamate, GABA, **dopamine**, and acetylch[redacted]ne can be identified by immunocytochemistry, RT-PCR, and calcium imaging in mass cultures. Individual NRPs also generate heterogeneous progeny as assessed by neurotransmitter response and synthesis, demonstrating the multipotent nature of the precursor cells. Differentiation can be modulated by sonic **hedgehog** (Shh) and bone morphogenetic protein (BMP)-2/4 molecules. Shh acts as a mitogen and inhibits differentiation (including cholinergic differentiation). BMP-2 and BMP-4, in contrast, inhibit cell division and promote differentiation (including cholinergic differentiation). Thus, a single neuronal precursor cell can differentiate into multiple classes of neurons, and this differentiation can be modulated by environmental signals.

L4 ANSWER 25 OF 44 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 1998188321 MEDLINE
DOCUMENT NUMBER: 98188321 PubMed ID: 9520484
TITLE: Nurr1 is essential for the induction of the **dopaminergic** phenotype and the survival of ventral mesencephalic late **dopaminergic** precursor neurons.
AUTHOR: Saucedo-Cardenas O; Quintana-Hau J D; Le W D; Smidt M P; Cox J J; De Mayo F; Burbach J P; Conneely O M
CORPORATE SOURCE: Department of Cell Biology, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, USA.
CONTRACT NUMBER: DK-52429 (NIDDK)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Mar 31) 95 (7) 4013-8. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980514
Last Updated on STN: 19980514
Entered Medline: 19980501

AB Nurr1 is a member of the nuclear receptor superfamily of transcription factors that is expressed predominantly in the central nervous system, including developing and mature **dopaminergic** neurons. Recent studies have demonstrated that Nurr1 is essential for the induction of phenotypic markers of ventral mid-brain **dopaminergic** neurons whose generation is specified by the floor plate-derived morphogenic signal sonic **hedgehog** (SHH), but the precise role of Nurr1 in this differentiative pathway has not been established. To provide further insights into the role of Nurr1 in the final differentiation pathway, we have examined the fate of **dopamine** cell precursors in Nurr1 null mutant mice. Here we demonstrate that Nurr1 functions at the later stages of **dopamine** cell development to drive differentiation of ventral mesencephalic late **dopaminergic** precursor neurons. In the absence of Nurr1, neuroepithelial cells that give rise to **dopaminergic** neurons adopt a normal ventral localization and neuronal phenotype characterized by expression of the homeodomain transcription factor and mesencephalic marker, Ptx-3, at embryonic day 11.5. However, these late precursors fail to induce a **dopaminergic** phenotype, indicating that Nurr1 is essential for specifying commitment of mesencephalic precursors to the full **dopaminergic** phenotype. Further, as development progresses, these mid-brain **dopamine** precursor cells degenerate in the absence of Nurr1, resulting in loss of Ptx-3 expression and a concomitant increase in apoptosis of ventral midbrain neurons in newborn null mutant mice. Taken together, these data indicate that Nurr1 is essential for both survival and final differentiation of ventral mesencephalic late **dopaminergic** precursor neurons into a complete **dopaminergic** phenotype.

L4 ANSWER 26 OF 44 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 1998322229 MEDLINE
DOCUMENT NUMBER: 98322229 PubMed ID: 9655799

TITLE: [redacted]s required for induction of floor plate and adjacent cells, but not most ventral neuron[redacted]n the mouse central nervous system.
AUTHOR: Matise M P; Epstein D J; Park H L; Platt K A; Joyner A L
CORPORATE SOURCE: Developmental Genetics Program and Howard Hughes Medical Institute, and Department of Cell Biology and Physiology and Neuroscience, NYU Medical Center, New York, NY 10016, USA.
CONTRACT NUMBER: R01HD35768 (NICHD)
SOURCE: DEVELOPMENT, (1998 Aug) 125 (15) 2759-70.
Journal code: ECW; 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980910
Last Updated on STN: 19980910
Entered Medline: 19980831

AB Induction of the floor plate at the ventral midline of the neural tube is one of the earliest events in the establishment of dorsoventral (d/v) polarity in the vertebrate central nervous system (CNS). The secreted molecule, Sonic **hedgehog**, has been shown to be both necessary and sufficient for this induction. In vertebrates, several downstream components of this signalling pathway have been identified, including members of the Gli transcription factor family. In this study, we have examined d/v patterning of the CNS in Gli2 mouse mutants. We have found that the floor plate throughout the midbrain, hindbrain and spinal cord does not form in Gli2 homozygotes. Despite this, motoneurons and ventral interneurons form in their normal d/v positions at 9.5 to 12.5 days postcoitum (dpc). However, cells that are generated in the region flanking the floor plate, including **dopaminergic** and serotonergic neurons, were greatly reduced in number or absent in Gli2 homozygous embryos. These results suggest that early signals derived from the notochord can be sufficient for establishing the basic d/v domains of cell differentiation in the ventral spinal cord and hindbrain. Interestingly, the notochord in Gli2 mutants does not regress ventrally after 10.5 dpc, as in normal embryos. Finally, the spinal cord of Gli1/Gli2 zinc-finger-deletion double homozygous mutants appeared similar to Gli2 homozygotes, indicating that neither gene is required downstream of Shh for the early development of ventral cell fates outside the ventral midline.

L4 ANSWER 27 OF 44 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:65109 BIOSIS
DOCUMENT NUMBER: PREV199900065109
TITLE: Developmental and adult expression of sonic **hedgehog**, **patched** and smoothened mRNAs in rat brain.
AUTHOR(S): Traiffort, E. (1); Charytoniuk, D. A.; Watroba, L.; Faure, L. H.; Sales, N.; Ruat, M.
CORPORATE SOURCE: (1) INSERM Unit 334 SHFJ-CEA, 91401 Orsay France
SOURCE: Society for Neuroscience Abstracts, (1998) Vol. 24, No. 1-2, pp. 1031.
Meeting Info.: 28th Annual Meeting of the Society for Neuroscience, Part 1 Los Angeles, California, USA November 7-12, 1998 Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 28 OF 44 MEDLINE
ACCESSION NUMBER: 97468980 MEDLINE
DOCUMENT NUMBER: 97468980 PubMed ID: 9328045
TITLE: Specification and survival of **dopaminergic** neurons in the mammalian midbrain.
AUTHOR: Rosenthal A

CORPORATE SOURCE: [redacted]tment of Neuroscience, Genent[redacted]h, Inc., South San Francisco, California 94080, USA.[redacted]
SOURCE: ADVANCES IN PHARMACOLOGY, (1998) 42 908-11.
Journal code: AXI; 9015397. ISSN: 1054-3589.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971125

L4 ANSWER 29 OF 44 MEDLINE
ACCESSION NUMBER: 1998292174 MEDLINE
DOCUMENT NUMBER: 98292174 PubMed ID: 9630220
TITLE: FGF and Shh signals control **dopaminergic** and serotonergic cell fate in the anterior neural plate.
AUTHOR: Ye W; Shimamura K; Rubenstein J L; Hynes M A; Rosenthal A
CORPORATE SOURCE: Department of Neuroscience, Genentech, Inc., South San Francisco, California 94080, USA.
CONTRACT NUMBER: K02 MH01046-01.18. (NIMH)
SOURCE: CELL, (1998 May 29) 93 (5) 755-66.
Journal code: CQ4; 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980716
Last Updated on STN: 19980716
Entered Medline: 19980706

AB During development, distinct classes of neurons are specified in precise locations along the dorso-ventral and anterior-posterior axes of the neural tube. We provide evidence that intersections of Shh, which is expressed along the ventral neural tube, and FGF8, which is locally produced at the mid/hindbrain boundary and in the rostral forebrain, create induction sites for **dopaminergic** neurons in the midbrain and forebrain. The same intersection, when preceded by a third signal, FGF4, which is expressed in the primitive streak, defines an inductive center for hindbrain 5-HT neurons. These findings illustrate that cell patterning in the neural plate is a multistep process in which early inducers, which initially divide the neural plate into crude compartments, are replaced by multiple local organizing centers, which specify distinct neuronal cell types within these compartments.

L4 ANSWER 30 OF 44 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 97368243 MEDLINE
DOCUMENT NUMBER: 97368243 PubMed ID: 9221786
TITLE: Sonic **hedgehog** promotes the survival of specific CNS neuron populations and protects these cells from toxic insult In vitro.
AUTHOR: Miao N; Wang M; Ott J A; D'Alessandro J S; Woolf T M; Bumcrot D A; Mahanthappa N K; Pang K
CORPORATE SOURCE: Ontogeny, Inc., Cambridge, Massachusetts 02138, USA.
SOURCE: JOURNAL OF NEUROSCIENCE, (1997 Aug 1) 17 (15) 5891-9.
Journal code: JDF; 8102140. ISSN: 0270-6474.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971021
Last Updated on STN: 19971021
Entered Medline: 19971003

AB Sonic **hedgehog** (Shh), an axis-determining secreted protein, is expressed during early vertebrate embryogenesis in the notochord and ventral neural tube. In this site it plays a role in the phenotypic

specification of [redacted]ntral neurons along the length[redacted]f the CNS. For example,
Shh induces the differentiation of motor neurons in the spinal cord and **dopaminergic** neurons in the midbrain. Shh expression, however, persists beyond this induction period, and we have asked whether the protein shows novel activities beyond phenotype specification. Using cultures derived from embryonic day 14.5 (E14. 5) rat ventral mesencephalon, we show that Shh is also trophic for **dopaminergic** neurons. Interestingly, Shh not only promotes **dopaminergic** neuron survival, but also promotes the survival of midbrain GABA-immunoreactive (GABA-ir) neurons. In cultures derived from the E15-16
striatum, Shh promotes the survival of GABA-ir interneurons to the exclusion of any other cell type. Cultures derived from E15-16 ventral spinal cord reveal that Shh is again trophic for interneurons, many of which are GABA-ir and some of which express the Lim-1/2 nuclear marker, but it does not appear to support motorneuron survival. Shh does not support the survival of sympathetic or dorsal root ganglion neurons. Finally, using the midbrain cultures, we show that in the presence of MPP+, a highly specific neurotoxin, Shh prevents **dopaminergic** neuron death that normally would have occurred. Thus Shh may have therapeutic value as a protective agent in neurodegenerative disease.

L4 ANSWER 31 OF 44 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:471736 BIOSIS
DOCUMENT NUMBER: PREV199799770939
TITLE: Sonic **hedgehog** is neurotrophic for specific CNS neuron populations in vitro.
AUTHOR(S): Miao, N.; Wang, M.; Ott, J. A.; D'Alessandro, J. S.; Platika, D.; Mahanthappa, N. K.; Pang, K.
CORPORATE SOURCE: Ontogeny Inc., 45 Moulton St., Cambridge, MA 02138 USA
SOURCE: Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 891.
Meeting Info.: 27th Annual Meeting of the Society for Neuroscience, Part 1 New Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L4 ANSWER 32 OF 44 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 97388426 MEDLINE
DOCUMENT NUMBER: 97388426 PubMed ID: 9247260
TITLE: Control of cell pattern in the neural tube by the zinc finger transcription factor and oncogene Gli-1.
AUTHOR: Hynes M; Stone D M; Dowd M; Pitts-Meek S; Goddard A; Gurney
A; Rosenthal A
CORPORATE SOURCE: Department of Neuroscience, Genentech, Inc., South San Francisco, California 94080, USA.
SOURCE: NEURON, (1997 Jul) 19 (1) 15-26.
Journal code: AN8; 8809320. ISSN: 0896-6273.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971013
Last Updated on STN: 19971013
Entered Medline: 19971002
AB Sonic **hedgehog** (Shh) is a putative morphogen secreted by the floor plate and notochord, which specifies the fate of multiple cell types
in the ventral aspect of the vertebrate nervous system. Since in Drosophila the actions of Hh have been shown to be transduced by Cubitus interruptus (Ci), a zinc finger transcription factor, we examined whether a vertebrate homolog of this protein can mediate the functions of Shh in the vertebrate nervous system. Here, we demonstrate that expression of Gli-1, one of three vertebrate homologs of Ci, can be induced by Shh in

the neural tube [redacted]ther, ectopic expression of G[redacted]-1 in the dorsal midbrain and hindbrain of transgenic mice mimics [redacted]e effects of ectopically expressed Shh-N, leading to the activation of ventral neural tube markers such as Ptc, HNF-3beta, and Shh; to the suppression of dorsal markers such as Pax-3 and AL-1; and to the formation of ectopic dorsal clusters of **dopaminergic** and serotonergic neurons. These findings demonstrate that GLI-1 can reproduce the cell patterning actions of Shh in the developing nervous system and provide support for the hypothesis that it is a mediator of the Shh signal in vertebrates.

L4 ANSWER 33 OF 44 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 96382468 MEDLINE
DOCUMENT NUMBER: 96382468 PubMed ID: 8790332
TITLE: Regulation of **patched** by sonic **hedgehog** in the developing neural tube.
AUTHOR: Marigo V; Tabin C J
CORPORATE SOURCE: Department of Genetics, Harvard Medical School, Boston, MA 02115, USA.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Sep 3) 93 (18) 9346-51. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961106
Last Updated on STN: 19990129
Entered Medline: 19961024
AB Ventral cell fates in the central nervous system are induced by Sonic **hedgehog**, a homolog of **hedgehog**, a secreted Drosophila protein. In the central nervous system, Sonic **hedgehog** has been identified as the signal inducing floor plate, motor neurons, and **dopaminergic** neurons. Sonic **hedgehog** is also involved in the induction of ventral cell type in the developing somites. ptc is a key gene in the Drosophila **hedgehog** signaling pathway where it is involved in transducing the **hedgehog** signal and is also a transcriptional target of the signal. PTC, a vertebrate homolog of this Drosophila gene, is genetically downstream of Sonic **hedgehog** (Shh) in the limb bud. We analyze PTC expression during chicken neural and somite development and find it expressed in all regions of these tissues known to be responsive to Sonic **hedgehog** signal. As in the limb bud, ectopic expression of Sonic **hedgehog** leads to ectopic induction of PTC in the neural tube and paraxial mesoderm. This conservation of regulation allows us to use PTC as a marker for Sonic **hedgehog** response. The pattern of PTC expression suggests that Sonic **hedgehog** may play an inductive role in more dorsal regions of the neural tube than have been previously demonstrated. Examination of the pattern of PTC expression also suggests that PTC may act in a negative feedback loop to attenuate **hedgehog** signaling.

L4 ANSWER 34 OF 44 MEDLINE
ACCESSION NUMBER: 97040381 MEDLINE
DOCUMENT NUMBER: 97040381 PubMed ID: 8885719
TITLE: Epigenetic factors and midbrain **dopaminergic** neurone development.
AUTHOR: Perrone-Capano C; di Porzio U
CORPORATE SOURCE: International Institute of Genetics and Biophysics, Consiglio Nazionale delle Ricerche, Naples, Italy.
SOURCE: BIOESSAYS, (1996 Oct) 18 (10) 817-24. Ref: 60
Journal code: 9YY; 8510851. ISSN: 0265-9247.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: [redacted]sh
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961216

AB In the mammalian brain **dopamine** systems play a central role in the control of movement, hormone release, emotional balance and reward. Alteration of **dopaminergic** neurotransmission is involved in **Parkinson**'s disease and other movement disorders, as well as in some psychotic syndromes. This review summarises recent findings, which shed some light on signals and cellular interactions involved in the specification and maturation of the **dopaminergic** function during neurogenesis. In particular we will focus on three major issues: (1) the differentiation of **dopaminergic** neurones triggered by direct contact with the midbrain floor plate cells through the action of sonic **hedgehog**; (2) the neurotrophic factors acting on **dopaminergic** neurones; and (3) the role of target striatal cells on the survival and the axonal growth of developing or grafted **dopaminergic** neurones.

L4 ANSWER 35 OF 44 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 97109392 MEDLINE
DOCUMENT NUMBER: 97109392 PubMed ID: 8951672
TITLE: Regulation of connexin-43, GFAP, and FGF-2 is not accompanied by changes in astroglial coupling in MPTP-lesioned, FGF-2-treated **parkinsonian** mice.
AUTHOR: Rufer M; Wirth S B; Hofer A; Dermietzel R; Pastor A; Kettenmann H; Unsicker K
CORPORATE SOURCE: Department of Anatomy and Cell Biology, University of Heidelberg, Germany.
SOURCE: JOURNAL OF NEUROSCIENCE RESEARCH, (1996 Dec 1) 46 (5) 606-17.
Journal code: KAC; 7600111. ISSN: 0360-4012.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970424
Last Updated on STN: 20000303
Entered Medline: 19970414

AB Basic fibroblast growth factor (bFGF; FGF-2) has potent trophic effects on developing and toxically impaired midbrain **dopaminergic** (DAergic) neurons which are crucially affected in **Parkinson**'s disease. The trophic effects of FGF-2 are largely indirect, both in vitro and in vivo, and possibly involve intermediate actions of astrocytes and other glial cells. To further investigate the cellular and molecular mechanisms underlying the restorative actions of FGF-2, and to analyse in more detail the changes within astroglial cells in the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-lesioned striatum, we have studied striatal expression and regulation of connexin-43 (cx43), the principal gap junction protein of astroglial cells, along with the expression of glial fibrillary acidic protein (GFAP), FGF-2, and functional coupling. Our results show an immediate, yet transient increase in cx43 mRNA, and a sustained increase in FGF-2 mRNA, GFAP-positive cells, and cx43-immunoreactive punctata following the MPTP lesion, without any induction of functional coupling between astrocytes and other glial cells as revealed by dye coupling of **patched** cells. Unilateral administration of FGF-2 in a piece of gelfoam caused a further increase in cx43-positive punctata immediately adjacent to the implant, which was more pronounced than after application of a gelfoam containing the nontrophic control protein cytochrome C. These changes were parallelled by a small increase in cx43 protein determined by Western blot, but not by

alterations in [redacted]oupling state of cells in the [redacted]icinity of the gelfoam implant. Although our data indicate that MPTP and [redacted]xogenous FGF-2 may alter expression and protein levels of cx43, they do not support the notion that increases in cellular coupling may underly the trophic and widespread actions of FGF-2 in the MPTP-model of **Parkinson**'s disease.

L4 ANSWER 36 OF 44 MEDLINE
ACCESSION NUMBER: 97026379 MEDLINE
DOCUMENT NUMBER: 97026379 PubMed ID: 8872557
TITLE: Noradrenergic and **dopaminergic** systems in the central nervous system of the **hedgehog** (Erinaceus europaeus).
AUTHOR: Michaloudi H C; Papadopoulos G C
CORPORATE SOURCE: Department of Anatomy, Veterinary School, University of Thessaloniki, Greece.
SOURCE: JOURNAL FUR HIRNFORSCHUNG, (1996) 37 (3) 319-50.
Journal code: ID3; 0421521. ISSN: 0021-8359.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19970106

AB The distribution of the noradrenaline (NA)- and **dopamine** (DA)-containing neuronal structures in the central nervous system of the **hedgehog** (Erinaceus europaeus), a phylogenetically old mammalian species, was immunocytochemically studied employing antibodies directed against the catecholamines (CA) themselves. Groups of DA cell bodies observed in this study were similar to those present in other species but the distributional map of the NA-containing cell bodies exhibited some peculiarities. Prominent among them were the absence of the A3 group and the paucity of CA cells in the A2 group. DA neurons in the hypothalamus, apart from the densely populated paraventricular and arcuate nuclei, were fewer and less widely distributed than in other species. In the **hedgehog** mesencepha- Ion, in contrast to what has been described in other species, the major DA cell group was present in the ventral tegmental area. CA immunoreactive fibers were widely distributed in the CNS of the **hedgehog**. However, similarly to what has been observed in other species, terminal fields of DA neurons were much more restricted when compared to those of the NA neurons. The neocortical DA projection system of the **hedgehog** appeared less developed but organized similar to that of the rat, and even less developed than that of the primates. The lack of profound regional and laminar variations in the density of cortical NA fibers in the **hedgehog** enhances the suggestion that the elaboration and differentiation of the NA cortical system parallels the phylogenetic development of the cortex. In the brainstem, interspecies differences in the distribution of the CA fibers were found to concern primarily some hypothalamic areas (medial preoptic area, suprachiasmatic nucleus, arcuate nucleus). Such differences in the thalamus concerned the NA innervation and they were notably present in the visual thalamic nuclei (dorsal lateral geniculate nucleus, lateral posterior thalamic nucleus). In the spinal cord, which was found to receive fewer CA afferents than those found in other species, the density of the DA fibers was much lower than that of the NA axons. In addition to the CNS areas that have been described in other species to receive catecholaminergic innervation, the present study showed that both types of catecholaminergic fibers are distributed in the choroid plexus and along the ventricular wall of the brain ventricles and the central canal of the **hedgehog**.

L4 ANSWER 37 OF 44 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 97041678 MEDLINE
DOCUMENT NUMBER: 97041678 PubMed ID: 8886949

TITLE: [redacted]holaminergic and serotoninerg[redacted] fibres innervate the ventricular system of the **hedgehog**[redacted]NS.
AUTHOR: Michaloudi H C; Papadopoulos G C
CORPORATE SOURCE: Department of Anatomy, Veterinary School, University of Thessaloniki, Greece.
SOURCE: JOURNAL OF ANATOMY, (1996 Oct) 189 (Pt 2) 273-83.
Journal code: HBB; 0137162. ISSN: 0021-8782.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970227
Last Updated on STN: 19970227
Entered Medline: 19970211

AB Immunocytochemistry with antisera against serotonin (5-HT), **dopamine** (DA) and noradrenaline (NA) was used to detect monoaminergic (MA) fibres in the ventricular system of the **hedgehog** Erinaceus europaeus. Light microscopic examination of immunocytochemically stained sections revealed that the ventricular system of the **hedgehog** is unique among mammals in that the choroid plexuses receive CA axons and that the supraependyma and subependyma of the cerebral ventricles and the spinal central canal are innervated both by serotoninergic and catecholaminergic (CA) fibres. Supraependymal 5-HT axons were generally more abundant and created at places a large number of interconnected basket-like structures, whereas CA fibres were usually directed towards the ventricular lumen. In the lateral ventricles, CA fibres were more numerous in the ependyma lining grey matter, whereas a higher 5-HT innervation density was observed in the area between the corpus callosum and the caudate nucleus or the septum. In the 3rd ventricle, the ependyma of its dorsal part exhibited a higher 5-HT and NA innervation density, whereas DA fibres were preferentially distributed in the ventral half of the basal region. The ependyma lining the cerebral aqueduct displayed a higher MA innervation density in its ventral part. The ependymal wall of the 4th ventricle exhibited an extremely dense 5-HT innervation, mainly in the floor of the ventricle, relatively fewer NA fibres and only sparse DA ones. Few NA and relatively more 5-HT fibres were detected in the ependyma of the central canal. Finally, the circumventricular organs were unevenly innervated by the 3 types of MA fibres. The extensive monoaminergic innervation of the **hedgehog** ventricular system described here probably reflects a transitory evolutionary stage in the phylogeny of the MA systems with presently unknown functional implications.

L4 ANSWER 38 OF 44 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:48033 BIOSIS
DOCUMENT NUMBER: PREV199799347236
TITLE: A neurotrophic activity of sonic **hedgehog** promotes the survival of **dopaminergic** neurons.
AUTHOR(S): Miao, N.; Wang, M.; Woolf, T. M.; Pang, K.
SOURCE: Cell Transplantation, (1996) Vol. 5, No. 5 SUPPL. 2, pp. 17.
Meeting Info.: Third International Congress of the Cell Transplant Society Miami Beach, Florida, USA September 29-October 2, 1996
ISSN: 0963-6897.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L4 ANSWER 39 OF 44 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 96071675 MEDLINE
DOCUMENT NUMBER: 96071675 PubMed ID: 7584992
TITLE: Induction of **dopaminergic** neuron phenotype in the midbrain by Sonic **hedgehog** protein.
AUTHOR: Wang M Z; Jin P; Bumcrot D A; Marigo V; McMahon A P; Wang E
A; Woolf T; Pang K

CORPORATE SOURCE: [redacted]geny, Inc., Cambridge, Massach[redacted]etts 02139, USA.
SOURCE: NATURE MEDICINE, (1995 Nov) 1 (11) [redacted]184-8.
Journal code: CG5; 9502015. ISSN: 1078-8956.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951228

AB Loss of substantia nigra **dopaminergic** neurons, which develop from the ventral region of the midbrain, is associated with **Parkinson**'s disease. During embryogenesis, induction of these and other ventral neurons is influenced by interactions with the induction of mesoderm of the notochord and the floor plate, which lies at the ventral midline of the developing CNS. Sonic **hedgehog** encodes a secreted peptide, which is expressed in notochord and floor plate cells and can induce appropriate ventral cell types in the basal forebrain and spinal cord. Here we demonstrate that Sonic **hedgehog** is sufficient to induce **dopaminergic** and other neuronal phenotypes in chick mesencephalic explants in vitro. We find that Sonic **hedgehog** is a general ventralizing signal in the CNS, the specific response being determined by the receiving cells. These results suggest that Sonic **hedgehog** may have utility in the induction of clinically important cell types.

L4 ANSWER 40 OF 44 MEDLINE
ACCESSION NUMBER: 95344779 MEDLINE
DOCUMENT NUMBER: 95344779 PubMed ID: 7619528
TITLE: Induction of midbrain **dopaminergic** neurons by Sonic **hedgehog**.
AUTHOR: Hynes M; Porter J A; Chiang C; Chang D; Tessier-Lavigne M; Beachy P A; Rosenthal A
CORPORATE SOURCE: Department of Neuroscience, Genentech, Inc., South San Francisco, California 94080, USA.
SOURCE: NEURON, (1995 Jul) 15 (1) 35-44.
Journal code: AN8; 8809320. ISSN: 0896-6273.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950911
Last Updated on STN: 19950911
Entered Medline: 19950825

AB Midbrain **dopaminergic** neurons, whose loss in adults results in **Parkinson**'s disease, can be specified during embryonic development by a contact-dependent signal from floor plate cells. Here we show that the amino-terminal product of Sonic **hedgehog** autoproteolysis (SHH-N), an inductive signal expressed by floor plate cells, can induce **dopaminergic** neurons in vitro. We show further that manipulations to increase the activity of cyclic AMP-dependent protein kinase A, which is known to antagonize **hedgehog** signaling, can block **dopaminergic** neuron induction by floor plate cells. Our results and those of other studies indicate that SHH-N can function in a dose-dependent manner to induce different cell types within the neural tube. Our results also provide the basis for a potential cell transplantation therapy for **Parkinson**'s disease.

L4 ANSWER 41 OF 44 MEDLINE DUPLICATE 20
ACCESSION NUMBER: 80223903 MEDLINE
DOCUMENT NUMBER: 80223903 PubMed ID: 7389377
TITLE: Catecholamines, ATP and **dopamine**-beta-hydroxylase in the adrenal medulla of the **hedgehog** in the prehibernating state and during hibernation.
AUTHOR: Helle K B; Bolstad G; Pihl K E; Knudsen R
SOURCE: CRYOBIOLOGY, (1980 Feb) 17 (1) 74-92.
Journal code: DT3; 0006252. ISSN: 0011-2240.

PUB. COUNTRY: [redacted]d States
Journal; Article; (JOURNAL ARTICL
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198009
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19970203
Entered Medline: 19800928

L4 ANSWER 42 OF 44 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1978:21899 BIOSIS
DOCUMENT NUMBER: BR14:21899
TITLE: RADIOAUTOGRAPHIC STUDIES OF AMINERGIC NEURONS TERMINATING IN THE MEDIAN EMINENCE.
AUTHOR(S): CALAS A
SOURCE: COSTA, ERMINIO AND G. L. GESSA (ED.). ADVANCES IN BIOCHEMICAL PSYCHOPHARMACOLOGY, VOL. 16. NONSTRIATAL DOPAMINERGIC NEURONS. XX+708P. ILLUS. RAVEN PRESS: NEW YORK, N.Y., USA, (1977) 79-88.
ISBN: 0-89004-127-.
FILE SEGMENT: BR; OLD
LANGUAGE: Unavailable

L4 ANSWER 43 OF 44 MEDLINE
ACCESSION NUMBER: 76001652 MEDLINE
DOCUMENT NUMBER: 76001652 PubMed ID: 808298
TITLE: [The effect of exogenous catecholamines on the cardiac rhythm and thermoregulation of hibernating hedgehogs (Erinaceus europaeus L.)].
Effets des catecholamines d'origine exogene sur le rythme cardiaque et la thermoregulation du Herisson (Erinaceus europaeus L.) en hibernation.
AUTHOR: Faure A
SOURCE: COMPTES RENDUS HEBDOMADAIRES DES SEANCES DE L ACADEMIE DES SCIENCES. D: SCIENCES NATURELLES, (1975 Jun 9) 280 (22) 2559-62.
Journal code: C9C; 7501107. ISSN: 0567-655X.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197511
ENTRY DATE: Entered STN: 19900313
Last Updated on STN: 19900313
Entered Medline: 19751120

AB No disturbance was seen either in cardiac rhythm or in temperature of hibernating **Hedgehog** (Erinaceus europaeus L.) after an isotonic saline injection, with the help of a permanent aortic indwelling catheter.

Partial or complete arousal was quickly obtained after increasing doses of norepinephrine (NE), while dihydroxyphenylalanine (L-**Dopa**), its natural precursor, induced the same effects more slowly. To differentiate the peripheral and central effects of L-**Dopa**, we used a pretreatment of Ro 4-4602, an inhibitor of the peripheral decarboxylation of L-**Dopa**; under these conditions we could not induce arousal in the hibernating animals. The arousals observed after NE and L-**Dopa** administration are suggested to be dependent upon a peripheral action of exogenous catecholamines, copying a natural mobilization of catecholamines reserves.

L4 ANSWER 44 OF 44 MEDLINE
ACCESSION NUMBER: 64043476 MEDLINE
DOCUMENT NUMBER: 64043476
TITLE: THE CATECHOLAMINE CONTENT OF THE BRAIN AND HEART OF THE **HEDGEHOG** (ERINACEUS EUROPAEUS) DURING HIBERNATION AND IN AN ACTIVE STATE.
AUTHOR: UUSPAEAE V J

SOURCE: [redacted]ES MEDICINAE EXPERIMENTALIS F[redacted]BIOLOGIAE FENNIAE, (1963) 41 340-8.
Journal code: 5F2. ISSN: 0003-4479.
PUB. COUNTRY: Finland
Journal
LANGUAGE: English
FILE SEGMENT: OLDMEDLINE
ENTRY MONTH: 196404
ENTRY DATE: Entered STN: 19990716
Last Updated on STN: 19990716

=> s GABA? huntington?

L5 0 GABA? HUNTINGTON?

=> s GABA? or huntington?

L6 90512 GABA? OR HUNTINGTON?

=> s l1 and l6

L7 24 L1 AND L6

=> dup rem l7

PROCESSING COMPLETED FOR L7
L8 15 DUP REM L7 (9 DUPLICATES REMOVED)

=> d ibib abs 1-15

L8 ANSWER 1 OF 15 BIOTECHNO COPYRIGHT 2001 Elsevier Science B.V.
ACCESSION NUMBER: 2001:32480293 BIOTECHNO
TITLE: Of flies and men - Studying human disease in Drosophila
AUTHOR: Bernards A.; Hariharan I.K.
CORPORATE SOURCE: A. Bernards, Massachusetts Gen. Hosp. Cancer Ctr., Building 149, 13th Street, Charlestown, MA 02129, United States.
E-mail: abernard@helix.mgh.harvard.edu
SOURCE: Current Opinion in Genetics and Development, (01 JUN 2001), 11/3 (274-278), 49 reference(s)
CODEN: COGDET ISSN: 0959-437X
DOCUMENT TYPE: Journal; General Review
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2001:32480293 BIOTECHNO
AB During the past year, the Drosophila genome has been sequenced. More than
60% of genes implicated in human disease have Drosophila orthologues. Developments in RNA-mediated interference and homologous recombination have made 'reverse genetics' feasible in Drosophila. Conventional Drosophila genetics is being used increasingly to place human disease genes of unknown function in the context of functional pathways.

L8 ANSWER 2 OF 15 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001091541 MEDLINE
DOCUMENT NUMBER: 20515603 PubMed ID: 11060228
TITLE: The Gsh2 homeodomain gene controls multiple aspects of telencephalic development.
AUTHOR: Corbin J G; Gaiano N; Machold R P; Langston A; Fishell G
CORPORATE SOURCE: Developmental Genetics Program and the Department of Cell Biology, The Skirball Institute of Biomolecular Medicine, New York University Medical Center, New York, NY 10016, USA.. fishell@saturn.med.nyu.edu
CONTRACT NUMBER: NS10962-01 (NINDS)
NS39007 (NINDS)

SOURCE: [redacted]OPMENT, (2000 Dec) 127 (23) [redacted]7-20.
Journal code: ECW. ISSN: 0950-199[redacted]
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered PubMed: 20001226
Entered Medline: 20010125

AB Homeobox genes have recently been demonstrated to be important for the proper patterning of the mammalian telencephalon. One of these genes is Gsh2, whose expression in the forebrain is restricted to the ventral domain. In this study, we demonstrate that Gsh2 is a downstream target of sonic **hedgehog** and that lack of Gsh2 results in profound defects in telencephalic development. Gsh2 mutants have a significant decrease in the expression of numerous genes that mark early development of the lateral ganglionic eminence, the striatal anlage. Accompanying this early loss of patterning genes is an initial expansion of dorsal telencephalic markers across the cortical-striatal boundary into the lateral ganglionic eminence. Interestingly, as development proceeds, there is compensation for this early loss of markers that is coincident with a molecular re-establishment of the cortical-striatal boundary. Despite this compensation, there is a defect in the development of distinct subpopulations of striatal neurons. Moreover, while our analysis suggests that the migration of the ventrally derived interneurons to the developing cerebral cortex is not significantly affected in Gsh2 mutants, there is a distinct delay in the appearance of **GABAergic** interneurons in the olfactory bulb. Taken together, our data support a model in which Gsh2, in response to sonic **hedgehog** signaling, plays a crucial role in multiple aspects of telencephalic development.

L8 ANSWER 3 OF 15 MEDLINE
ACCESSION NUMBER: 2000456126 MEDLINE
DOCUMENT NUMBER: 20296936 PubMed ID: 10835609
TITLE: Efficient generation of midbrain and hindbrain neurons from mouse embryonic stem cells.
AUTHOR: Lee S H; Lumelsky N; Studer L; Auerbach J M; McKay R D
CORPORATE SOURCE: Laboratory of Molecular Biology, NINDS, NIH, Bethesda, MD 20892, USA.
SOURCE: NATURE BIOTECHNOLOGY, (2000 Jun) 18 (6) 675-9.
Journal code: CQ3; 9604648. ISSN: 1087-0156.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001005
Last Updated on STN: 20001005
Entered Medline: 20000925

AB Embryonic stem (ES) cells are clonal cell lines derived from the inner cell mass of the developing blastocyst that can proliferate extensively in vitro and are capable of adopting all the cell fates in a developing embryo. Clinical interest in the use of ES cells has been stimulated by studies showing that isolated human cells with ES properties from the inner cell mass or developing germ cells can provide a source of somatic precursors. Previous studies have defined in vitro conditions for promoting the development of specific somatic fates, specifically, hematopoietic, mesodermal, and neurectodermal. In this study, we present a method for obtaining dopaminergic (DA) and serotonergic neurons in high yield from mouse ES cells in vitro. Furthermore, we demonstrate that the ES cells can be obtained in unlimited numbers and that these neuron types are generated efficiently. We generated CNS progenitor populations from ES

cells, expanded [redacted]e cells and promoted their di[redacted]erentiation into dopaminergic and serotonergic neurons in the pres[redacted]ce of mitogen and specific signaling molecules. The differentiation and maturation of neuronal cells was completed after mitogen withdrawal from the growth medium. This experimental system provides a powerful tool for analyzing the molecular mechanisms controlling the functions of these neurons in vitro and in vivo, and potentially for understanding and treating neurodegenerative and psychiatric diseases.

L8 ANSWER 4 OF 15 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2000168947 MEDLINE
DOCUMENT NUMBER: 20168947 PubMed ID: 10706430
TITLE: Dimorphic features of the different alpha-containing **GABA**-A receptor subtypes in the cortico-basal ganglia system of two distantly related mammals (**hedgehog** and rat).
COMMENT: Erratum in: Exp Brain Res 2000 Feb;130(3):415-6
AUTHOR: Facciolo R M; Alo' R; Tavolaro R; Canonaco M; Franzoni M F
CORPORATE SOURCE: Ecology Department, University of Calabria, Cosenza, Italy.
SOURCE: EXPERIMENTAL BRAIN RESEARCH, (2000 Feb) 130 (3) 309-19. Journal code: EP2; 0043312. ISSN: 0014-4819.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000407
Last Updated on STN: 20000606
Entered Medline: 20000329

AB This investigation represents a first study dealing with the dimorphic differences of the main alpha-containing gamma-aminobutyric acid (**GABA**(A)) receptors in the brain of two distantly related mammals (**hedgehog** and rat). The labeling of these receptors in the presence of zolpidem (highly selective benzodiazepine agonist) and under the different degree of **GABA**(A)/benzodiazepine allosteric coupling activities accounted for a heterogeneous colocalization of alpha1-enriched and of alpha2/3-enriched and alpha5-enriched **GABA**(A) receptors in some areas of the cortico-basal ganglia system (including the important ventrolateral thalamic station) of both mammalian sexes. In the **hedgehog**, the greatest (P<0.001) **GABA**-dependent reduction of zolpidem inhibition constants was mostly registered in alpha1- and/or alpha5-enriched areas, such as the frontoparietal cortex lamina III (235%), ventrolateral thalamic nucleus (128%), and substantia nigra pars reticulata (110%) of the male. However, the greatest reductions in the rat were instead detected in the male substantia nigra pars reticulata (192%) and female striatum (120%), areas which are enriched either by the colocalization of alpha1- with alpha2/3-subunits or by all three alpha-subunits. These results support the contention that a sex-related alpha-containing **GABA**(A) receptor sensitivity constitutes an important element in the execution of skilled motor activities during the different socio-sexual behaviors of the two mammals.

L8 ANSWER 5 OF 15 MEDLINE
ACCESSION NUMBER: 1999396701 MEDLINE
DOCUMENT NUMBER: 99396701 PubMed ID: 10393115
TITLE: Loss of Nkx2.1 homeobox gene function results in a ventral to dorsal molecular respecification within the basal telencephalon: evidence for a transformation of the pallidum into the striatum.
AUTHOR: Sussel L; Marin O; Kimura S; Rubenstein J L
CORPORATE SOURCE: Center for Neurobiology and Psychiatry, Department of Psychiatry and University of California at San Francisco, CA 94143-0984, USA.
CONTRACT NUMBER: K02 MH01046-01 (NIMH)

SOURCE: [redacted]OPMENT, (1999 Aug) 126 (15) 3[redacted]9-70.
Journal code: ECW; 8701744. ISSN: [redacted]50-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991005
Last Updated on STN: 19991005
Entered Medline: 19990921

AB The telencephalon is organized into distinct longitudinal domains: the cerebral cortex and the basal ganglia. The basal ganglia primarily consists of a dorsal region (striatum) and a ventral region (pallidum). Within the telencephalon, the anlage of the pallidum expresses the Nkx2.1 homeobox gene. A mouse deficient in Nkx2.1 function does not form pallidal structures, lacks basal forebrain TrkA-positive neurons (probable cholinergic neurons) and has reduced numbers of cortical cells expressing **GABA**, DLX2 and calbindin that migrate from the pallidum through the striatum and into the cortex. We present evidence that these phenotypes result from a ventral-to-dorsal transformation of the pallidal primordium into a striatal-like anlage.

L8 ANSWER 6 OF 15 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:450572 BIOSIS
DOCUMENT NUMBER: PREV199900450572
TITLE: Phylogenetic value of **GABAA** receptor subtypes in some limbic areas of an early appearing mammal.
AUTHOR(S): Facciolo, R. M. (1); Alo, R. (1); Canonaco, M. C. (1)
CORPORATE SOURCE: (1) Comparative Anatomy Lab., Ecology Dept., University of Calabria, Arcavacata Di Rende (CS), 87030 Italy
SOURCE: Comparative Biochemistry and Physiology Part A Molecular & Integrative Physiology, (Aug., 1999) Vol. 124, No. SUPPL., pp. S70.
Meeting Info.: Fifth International Congress of Comparative Physiology and Biochemistry Calgary, Alberta, Canada August 23-28, 1999
ISSN: 1095-6433.
DOCUMENT TYPE: Conference
LANGUAGE: English

L8 ANSWER 7 OF 15 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999115779 MEDLINE
DOCUMENT NUMBER: 99115779 PubMed ID: 9914262
TITLE: Cultured insect mushroom body neurons express functional receptors for acetylcholine, **GABA**, glutamate, octopamine, and dopamine.
AUTHOR: Cayre M; Buckingham S D; Yagodin S; Sattelle D B
CORPORATE SOURCE: Babraham Institute Laboratory of Molecular Signalling, Department of Zoology, University of Cambridge, Cambridge CB2 3EJ, United Kingdom.
SOURCE: JOURNAL OF NEUROPHYSIOLOGY, (1999 Jan) 81 (1) 1-14.
Journal code: JC7; 0375404. ISSN: 0022-3077.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990402
Last Updated on STN: 19990402
Entered Medline: 19990322

AB Fluorescence calcium imaging with fura-2 and whole cell, patch-clamp electrophysiology was applied to cultured Kenyon cells (interneurons) isolated from the mushroom bodies of adult crickets (Acheta domesticus) to demonstrate the presence of functional neurotransmitter receptors. In all cells investigated, 5 microM acetylcholine (ACh, n = 52) evoked an increase in intracellular free calcium ([Ca2+]i). Similar effects were

observed in resp[redacted] to 10 microM nicotine. The A[redacted] response was insensitive to atropine (50 microM) but was reduc[redacted] by mecamylamine (50 microM) and alpha-bungarotoxin (alpha-bgt, 10 microM). ACh-induced inward ion currents (n = 28, EACh approximately 0 mV) were also blocked by 1 microM mecamylamine and by 1 microM alpha-bgt. Nicotine-induced inward currents desensitized more rapidly than ACh responses. Thus functional alpha-bgt-sensitive nicotinic ACh receptors are abundant on all Kenyon cells tested, and their activation leads to an increase in [Ca2+]i. gamma-Aminobutyric acid (**GABA**, 100 microM) triggered a sustained decrease in [Ca2+]i. Similar responses were seen with a **GABAA** agonist, muscimol (100 microM), and a **GABAB** agonist, 3-APPA (1 mM), suggesting that more than one type of **GABA** receptor can affect [Ca2+]i. This action of **GABA** was not observed when the extracellular KCl concentration was lowered. All cells tested (n = 26) with patch-clamp electrophysiology showed picrotoxinin (PTX)-sensitive, **GABA**-induced (30-100 microM) currents with a chloride-sensitive reversal potential. Thus, an ionotropic PTX-sensitive **GABA** receptor was found on all Kenyon cells tested. Most (61%) of the 54 cells studied responded to -glutamate (100 microM) application either with a biphasic increase in [Ca2+]i or with a single, delayed, sustained [Ca2+]i increase. Nearly all cells tested (95%, n = 19) responded to (100 microM) -glutamate with rapidly desensitizing, inward currents that reversed at approximately -30 mV. Dopamine (100 microM) elicited either a rapid or a delayed increase in [Ca2+]i in 63% of the 26 cells tested. The time course of these responses varied greatly among cells. Dopamine failed to elicit currents in patch-clamped cells (n = 4). A brief decrease in [Ca2+]i was induced by octopamine (100 microM) in approximately 54% of the cells tested (n = 35). However, when extracellular CaCl2 was lowered, octopamine triggered a substantial increase in [Ca2+]i in 35% of the cells tested (n = 26). No octopamine-elicited currents were detected in **patched** -clamped cells (n = 10).

L8 ANSWER 8 OF 15 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1998414555 MEDLINE
DOCUMENT NUMBER: 98414555 PubMed ID: 9742154
TITLE: Spinal cord neuronal precursors generate multiple neuronal phenotypes in culture.
AUTHOR: Kalyani A J; Piper D; Mujtaba T; Lucero M T; Rao M S
CORPORATE SOURCE: Department of Neurobiology and Anatomy, University of Utah School of Medicine, Salt Lake City, Utah 84132, USA.
CONTRACT NUMBER: NO1-HD-7-3263 (NICHD)
SOURCE: JOURNAL OF NEUROSCIENCE, (1998 Oct 1) 18 (19) 7856-68. Journal code: JDF; 8102140. ISSN: 0270-6474.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981021
Last Updated on STN: 19981021
Entered Medline: 19981009

AB Neuronal restricted precursors (NRPs) () can generate multiple neurotransmitter phenotypes during maturation in culture. Undifferentiated E-NCAM+ (embryonic neural cell adhesion molecule) immunoreactive NRPs are mitotically active and electrically immature, and they express only a subset of neuronal markers. Fully mature cells are postmitotic, process-bearing cells that are neurofilament-M and synaptophysin immunoreactive, and they synthesize and respond to different subsets of neurotransmitter molecules. Mature neurons that synthesize and respond to glycine, glutamate, **GABA**, dopamine, and acetylcholine can be identified by immunocytochemistry, RT-PCR, and calcium imaging in mass cultures. Individual NRPs also generate heterogeneous progeny as assessed by neurotransmitter response and synthesis, demonstrating the multipotent nature of the precursor cells. Differentiation can be modulated by sonic **hedgehog** (Shh) and bone morphogenetic protein (BMP)-2/4 molecules. Shh acts as a mitogen and inhibits differentiation (including cholinergic

differentiation [redacted]MP-2 and BMP-4, in contrast, [redacted]ibit cell division and promote differentiation (including cholinergic d[redacted]erentiation). Thus, a single neuronal precursor cell can differentiate into multiple classes of neurons, and this differentiation can be modulated by environmental signals.

L8 ANSWER 9 OF 15 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 97368243 MEDLINE
DOCUMENT NUMBER: 97368243 PubMed ID: 9221786
TITLE: Sonic **hedgehog** promotes the survival of specific CNS neuron populations and protects these cells from toxic insult In vitro.
AUTHOR: Miao N; Wang M; Ott J A; D'Alessandro J S; Woolf T M; Bumcrot D A; Mahanthappa N K; Pang K
CORPORATE SOURCE: Ontogeny, Inc., Cambridge, Massachusetts 02138, USA.
SOURCE: JOURNAL OF NEUROSCIENCE, (1997 Aug 1) 17 (15) 5891-9. Journal code: JDF; 8102140. ISSN: 0270-6474.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971021
Last Updated on STN: 19971021
Entered Medline: 19971003
AB Sonic **hedgehog** (Shh), an axis-determining secreted protein, is expressed during early vertebrate embryogenesis in the notochord and ventral neural tube. In this site it plays a role in the phenotypic specification of ventral neurons along the length of the CNS. For example,
Shh induces the differentiation of motor neurons in the spinal cord and dopaminergic neurons in the midbrain. Shh expression, however, persists beyond this induction period, and we have asked whether the protein shows novel activities beyond phenotype specification. Using cultures derived from embryonic day 14.5 (E14. 5) rat ventral mesencephalon, we show that Shh is also trophic for dopaminergic neurons. Interestingly, Shh not only promotes dopaminergic neuron survival, but also promotes the survival of midbrain **GABA**-immunoreactive (**GABA**-ir) neurons. In cultures derived from the E15-16 striatum, Shh promotes the survival of **GABA**-ir interneurons to the exclusion of any other cell type. Cultures derived from E15-16 ventral spinal cord reveal that Shh is again trophic for interneurons, many of which are **GABA**-ir and some of which express the Lim-1/2 nuclear marker, but it does not appear to support motorneuron survival. Shh does not support the survival of sympathetic or dorsal root ganglion neurons. Finally, using the midbrain cultures, we show that in the presence of MPP+, a highly specific neurotoxin, Shh prevents dopaminergic neuron death that normally would have occurred. Thus Shh may have therapeutic value as a protective agent in neurodegenerative disease.

L8 ANSWER 10 OF 15 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:471736 BIOSIS
DOCUMENT NUMBER: PREV199799770939
TITLE: Sonic **hedgehog** is neurotrophic for specific CNS neuron populations in vitro.
AUTHOR(S): Miao, N.; Wang, M.; Ott, J. A.; D'Alessandro, J. S.; Platika, D.; Mahanthappa, N. K.; Pang, K.
CORPORATE SOURCE: Ontogeny Inc., 45 Moulton St., Cambridge, MA 02138 USA
SOURCE: Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 891.
Meeting Info.: 27th Annual Meeting of the Society for Neuroscience, Part 1 New Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L8 ANSWER 11 OF 15 MEDLINE
ACCESSION NUMBER: 96433249 MEDLINE

DOCUMENT NUMBER: [redacted]249 PubMed ID: 8836236
TITLE: Properties of spontaneous inhibit[redacted]synaptic currents in cultured rat spinal cord and medullary neurons.
AUTHOR: Lewis C A; Faber D S
CORPORATE SOURCE: Department of Anatomy and Neurobiology, Medical College of Pennsylvania, Philadelphia, USA.
CONTRACT NUMBER: NS-21848 (NINDS)
NS-27016 (NINDS)
SOURCE: JOURNAL OF NEUROPHYSIOLOGY, (1996 Jul) 76 (1) 448-60.
Journal code: JC7; 0375404. ISSN: 0022-3077.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961231

AB 1. To identify the type(s) and properties of inhibitory postsynaptic receptor(s) involved in synaptic transmission in cultured rat embryonic spinal cord and medullary neurons, we have used whole cell patch-clamp techniques to record miniature inhibitory postsynaptic currents (mIPSCs) in the presence of tetrodotoxin, DL-2-amino-5-phosphonovaleric acid, and 6-cyano-7-nitroquinoxaline-2,3-dione. 2. The mIPSCs recorded from both spinal cord and medullary neurons had skewed amplitude distributions. 3. The glycinergic antagonist strychnine and the **GABAergic** antagonist bicuculline each decreased both the frequency and mean peak amplitudes of mIPSCs. We conclude that both glycine and gamma-aminobutyric acid (**GABA**) are neurotransmitters at inhibitory synapses in our cultured cells. 4. Most (approximately 96-97%) mIPSCs decay with single-exponential time constants, and decay time distributions were consistently best fitted by the sum of four Gaussians with decay constants as follows: D1 = 5.8 +/- 0.1 (SE) ms (n = 63), D2 = 12.2 +/- 0.2 ms (n = 61), D3 = 23.2 +/- 0.4 ms (n = 54), and D4 = 44.7 +/- 1.0 ms (n = 57). We conclude that the four classes of decay times represent kinetically different inhibitory postsynaptic receptor populations. 5. Strychnine and bicuculline usually had one of two different effects on the mIPSC decay time constant distributions; either selective decreases in the frequency of mIPSCs with decay times in certain classes (i.e., the D1 class was reduced by bicuculline, the D2 class by strychnine, and the D3 and D4 classes by both antagonists) or a nonselective depression in the frequency of mIPSCs with decay times in all four classes. The particular effect observed in a given neuron was correlated with the presence or absence of ATP and guanosine 5'-triphosphate (GTP) in the patch pipette. Namely, in 71% of the antagonist applications where the pipette contained ATP and GTP, the result was a nonselective decrease in mIPSCs in all decay time constant classes. Conversely, in 54% of the antagonist applications in their absence, the result was a selective decrease in the frequency of mIPSCs in specific decay time constant classes. 6. In some experiments, mIPSCs reappeared in antagonist solution after an essentially complete block. Recovery from block in the continued presence of antagonist was never observed in the absence of ATP and GTP (8 neurons), and, at the same time, 5 of 9 neurons **patched** with ATP and GTP in the pipette did show recovery (56%).

L8 ANSWER 12 OF 15 MEDLINE
ACCESSION NUMBER: 95294847 MEDLINE
DOCUMENT NUMBER: 95294847 PubMed ID: 7776231
TITLE: Synaptic integration in layer IV of the ferret striate cortex.
AUTHOR: Hirsch J A
CORPORATE SOURCE: Laboratory of Neurobiology, New York, NY 10021, USA.
CONTRACT NUMBER: EY05253 (NEI)
EY09593 (NEI)
SOURCE: JOURNAL OF PHYSIOLOGY, (1995 Feb 15) 483 (Pt 1) 183-99.

[redacted]al code: JQV; 0266262. ISSN: [redacted]22-3751.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199507
ENTRY DATE: Entered STN: 19950720
Last Updated on STN: 19960129
Entered Medline: 19950712

AB 1. Whole-cell patch recording were made with dye-filled electrodes from layer IV in slices of the ferret striate cortex. Projections from the thalamus and layer VI provide most of the extralaminar input to layer IV. Interactions between these two pathways are thought to play a role in the generation of suppressive non-linearities such as end-inhibition. Thus, synaptic responses evoked by stimulating each pathway individually were compared with those produced by activating both projections together. 2. Spiny stellate cells are the majority population in layer IV and were the most frequently **patched** neurons (n = 23); all fired adapting trains of large, fast action potentials. About half of those tested (n = 13) were progressively inhibited by strengthening the stimulus to layer VI, while the rest became more excited. For the former, the response evoked by stimulating both pathways in coincidence was often more hyperpolarizing than would have been predicted by summing the responses to either projection alone (n = 4). Hence, the inputs from the thalamus and layer VI are integrated by circuits that can produce strong and non-linear inhibition. 3. Recordings from various basket cells, which are inhibitory, have provided a first view of the suppressive circuits in layer IV (n = 5). Two cells were excited by stimulation of both pathways. The remaining three cells were mainly excited by activation of thalamic afferents but were largely inhibited by stimulation of layer VI. Thus, inhibition seen at the level of the spiny stellate cells could result from two mechanisms operating via presynaptic smooth cells: convergent excitation provided by both ascending pathways on the one hand, and a push-pull relationship between pathways on the other.

L8 ANSWER 13 OF 15 MEDLINE
ACCESSION NUMBER: 93029416 MEDLINE
DOCUMENT NUMBER: 93029416 PubMed ID: 1410413
TITLE: Cytochemistry of CSF-contacting neurons and pinealocytes.
AUTHOR: Vigh B; Vigh-Teichmann I
CORPORATE SOURCE: 2nd Department of Anatomy, Semmelweis University Medical School, Budapest, Hungary.
SOURCE: PROGRESS IN BRAIN RESEARCH, (1992) 91 299-306. Ref: 21
Journal code: Q0B; 0376441. ISSN: 0079-6123.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199211
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19970203
Entered Medline: 19921125

AB Gamma aminobutyric acid (**GABA**)-immunoreactive neurons of the paraventricular organ of the bony fish Coregonus albus send dendrites into the third ventricle. Their axons run to the synaptic zone of the infundibular lobe. The dendrites may take up some chemical information from the third ventricle, while the axons communicate it to the neuropil of the hypothalamus perhaps to modify its activity according to the state of the CSF. Serotonin-immunoreactive CSF-contacting neurons in the spinal cord of the hagfish Myxine glutinosa from dendrite terminals in the central canal and bear stereocilia like known mechanoreceptors. The Reissner's fiber runs above the stereocilia and flows out from the central

canal through i[redacted]udal opening. Possibly, the [redacted]r keeps open this aperture and ensures the flow of the CSF, which m[redacted]serve as a mechanoreceptory input for the CSF-contacting neurons. In the pineal recess of **hedgehog**, CSF-contacting pinealocytes develop enlarged cilia corresponding to the photoreceptor outer segments of submammalian pinealocytes. Potassium pyroantimonate cytochemistry shows a similar localization of calcium ions in the mammalian pinealocyte as in the submammalian photoreceptor ones. Pineal calcifications are present in some birds (goose, duck) and may be connected to the photoreceptory Ca-exchange of the pineal organ. Axonic processes of pinealocytes form synapses on secondary neurons in mammals (**hedgehog**, rat, cat). Such neurons are also present in human pineals. Axons of these neurons constitute a pinealofugal pathway. In the cat, some of the intrinsic pineal neurons are **GABA**-immunoreactive, they form axodendritic and axo-axonic synapses (inhibitory?) on immunonegative neurons and pinealocytes, respectively. (ABSTRACT TRUNCATED AT 250 WORDS)

L8 ANSWER 14 OF 15 MEDLINE

ACCESSION NUMBER: 92297974 MEDLINE
DOCUMENT NUMBER: 92297974 PubMed ID: 1351408
TITLE: Immunocytochemistry and calcium cytochemistry of the mammalian pineal organ: a comparison with retina and submammalian pineal organs.
AUTHOR: Vigh-Teichmann I; Vigh B
CORPORATE SOURCE: Neuroendocrine Section, Hungarian Academy of Sciences, Semmelweis University Medical School, Budapest.
SOURCE: MICROSCOPY RESEARCH AND TECHNIQUE, (1992 May 1) 21 (3) 227-41. Ref: 141
Journal code: BAG; 9203012. ISSN: 1059-910X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199207
ENTRY DATE: Entered STN: 19920731
Last Updated on STN: 19970203
Entered Medline: 19920723

AB Morphologically the mammalian pineal organ is a part of the diencephalon. It represents a neural tissue histologically ("pineal nervous tissue") and is dissimilar to endocrine glands. Submammalian pinealocytes resemble the photoreceptor cells of the retina, and some of their cytologic characteristics are preserved in the mammalian pinealocytes together with compounds demonstrable by cyto- and immunocytochemistry and participating in photochemical transduction. In our opinion, the main trend of today's literature on pineal functions--only considering the organ as a common endocrine gland--deviates from this structural and histochemical basis. In mammals, similar to the lower vertebrates, the pinealocytes have a sensory cilium developed to a different extent. The axonic processes of pinealocytes form ribbon-containing synapses on secondary pineal neurons, and/or neurohormonal terminals on the basal lamina of the surface of the pineal nervous tissue facing the perivascular spaces. Ribbon-containing axo-dendritic synapses were found in the rat, cat, guinea pig, ferret, and **hedgehog**. In the cat, we found **GABA**-immunoreactive interneurons, while the secondary nerve cells, whose axons enter the habenular commissure, were **GABA**-immunonegative. **GABA** -immunogold-labeled axons run between pinealocytes and form axo-dendritic synapses on intrapineal neurons. There is a similarity between the light and electron microscopic localization of Ca ions in the mammalian and submammalian pineal organs and retina of various vertebrates. Calcium pyroantimonate deposits--showing the presence of Ca ions--were found in

the outer segme[redacted]f the pineal and retinal pho[redacted]eceptors of the frog. In the rat and human pineal organ, calcium accum[redacted]ed on the plasmalemma of pinealocytes and intercellularly among pinealocytes. The formation of pineal concrements in mammals may be connected to the high need for Ca exchange of the pinealocytes for their supposed receptor and effector functions.

L8 ANSWER 15 OF 15 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 88033792 MEDLINE
DOCUMENT NUMBER: 88033792 PubMed ID: 3312309
TITLE: VIP- and CCK-like-immunoreactive neurons in the **hedgehog** (Erinaceus europaeus) and sheep (Ovis aries) brain.
AUTHOR: Antonopoulos J; Papadopoulos G C; Karamanlidis A N; Parnavelas J G; Dinopoulos A; Michaloudi H
CORPORATE SOURCE: Department of Anatomy, School of Veterinary Medicine, University of Thessaloniki, Greece.
SOURCE: JOURNAL OF COMPARATIVE NEUROLOGY, (1987 Sep 8) 263 (2) 290-307.
Journal code: HUV; 0406041. ISSN: 0021-9967.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198711
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19871123

AB The distribution pattern and the morphology of vasoactive intestinal polypeptide (VIP)- and cholecystokinin (CCK)-like-immunoreactive neurons were studied in the brain of the **hedgehog** and the sheep by means of the peroxidase-antiperoxidase immunocytochemical method. A total of 34 hedgehogs and 26 sheep of both sexes were used. Fourteen hedgehogs and 13 sheep received an intracerebroventricular injection of colchicine that enhanced the immunostaining and revealed "new" immunoreactive cell bodies.

VIP-immunoreactive bipolar and multipolar neurons were observed in both species in the cerebral cortex, hippocampal formation, amygdaloid complex, hypothalamus, and central gray substance of the midbrain. CCK-immunoreactive bipolar, bitufted, and multipolar neurons displayed a broader distribution in both mammals than VIP neurons and were found in the cerebral cortex, the hippocampal formation, the amygdaloid complex, the hypothalamus, the mesencephalon, and the pons. In the cortex, in both the **hedgehog** and the sheep, VIP neurons were located in all layers but were concentrated in layers II and III, with the majority being typical bipolar. CCK neurons were more numerous in the superficial layers (I-III) but were found in the deep layers as well. They were bipolar, bitufted, or multipolar in morphology. From these neurons a small percentage, which were located almost exclusively in layers II and III of the visual cortex, exhibited also VIP immunoreactivity. Perikarya of such double-labeled cells were ovoid or round in shape with one or two main processes emanating from each pole of the cell body and oriented perpendicularly to the pia. The coexistence of the two peptides within individual neurons of the cortex has not been reported in other species and its physiological significance is discussed in relation to the **GABAergic** neurons of the cortex.

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